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Complete List of Authors:	Jørgensen, Christoffer; Rigshopsitalet, Copenhagen University, Section for Surgical Pathophysiology Jacobsen, Michael; Aarhus University Hospital, Department of Orthopaedics Soballe, Kjeld; Aarhus University Hospital, Aarhus University, Department of Orthopaedics Hansen, Torben; Regional Hospital Holstebro, Aarhus University, Department of Orthopaedics Husted, Henrik; Hvidovre Hospital, Copenhagen University, Orthopaedic Department Kjaersgaard-Andersen, Per; Vejle Hospital, University of Southern Denmark, Department of Orthopedics Hansen, Lars; Sydvestjysk Hospital Esbjerg/Grindsted, Orthopedic Department Laursen, Mogens; Aalborg University Hospital, Aalborg University, Northern Orthopaedic Division Kehlet, Henrik; Rigshopsitalet, Copenhagen University, Section for Surgical Pathophysiology
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Thrombosis prophylaxis only during hospitalization in fast-track hip and knee arthroplasty, a prospective cohort study

Christoffer C Jørgensen*, Michael K Jacobsen, Kjeld Soeballe, Torben B Hansen, Henrik Husted, Per Kjærsgaard-Andersen, Lars T Hansen, Mogens B Laursen, and Henrik Kehlet

Section for Surgical Pathophysiology 4074, The Juliane Marie Centre, Rigshospitalet, Copenhagen University, 2100 Copenhagen, Denmark Christoffer C Jørgensen Research fellow

Department of Orthopaedics, Aarhus University Hospital, Aarhus University, Brendstrupgårdsvej 100, 8200 Aarhus N, Denmark Michael K Jacobsen Orthopaedic Surgeon

Department of Orthopaedics, Aarhus University Hospital, Aarhus University, Brendstrupgårdsvej 100, 8200 Aarhus N, Denmark Kjeld Soeballe Professor

Department of Orthopaedics, Regional Hospital Holstebro, Aarhus University, Lægårdvej 12 7500 Holstebro, Denmark Torben B Hansen Professor

Orthopaedic Department, Hvidovre University Hospital, Kettegård Alle 30, 2650 Hvidovre, Denmark Henrik Husted Senior Consultant

Department of Orthopedics, Vejle Hospital, University of Southern Denmark, Kabbeltoft 25, 7100 Vejle, Denmark Per Kjærsgaard-Andersen Associate Professor

Orthopaedic Department, Sydvestjysk Hospital Esbjerg/Grindsted, Engparken 1, 7200 Grindsted, Denmark Lars T Hansen Senior Consultant

Aalborg University Hospital Northern Orthopaedic Division, Aalborg University, Højgårdsvej 11, 9640 Farsø, Denmark Mogens B Laursen Associate Professor

Section for Surgical Pathophysiology 4074, The Juliane Marie Centre, Rigshospitalet, Copenhagen University, 2100 Copenhagen, Denmark Henrik Kehlet Professor

All authors are members of The Lundbeck Foundation Centre for Fast-track Hip and Knee Replacement 2100 Copenhagen, Denmark.

*Corresponding author: christoffer.calov.joergensen@regionh.dk Section for Surgical Pathophysiology 4074, The Juliane Marie Centre, Rigshospitalet, Copenhagen University, 2100 Copenhagen, Denmark

Abstract:

Objectives: International guidelines recommend thrombosis prophylaxis after total hip (THA) and knee arthroplasty (TKA) for up to 35 days. However previous studies often have hospital stays (LOS) of 8-12 days and not considering early mobilisation, which may reduce incidence of venous thromboembolic events (VTE). We investigated the incidence of any symptomatic thromboembolic events (TEE) with only in-hospital prophylaxis if LOS ≤5 days after fast-track THA and TKA.

Design: A prospective descriptive multicenter cohort study in fast-track THA and TKA from February 2010 to December 2011, with complete 90-days follow-up through the Danish National Patient Registry and patient files.

Setting: 6 Danish high-volume centers with a similar standardized fast-track setup, including spinal anaesthesia, opioid-sparing analgesia, early mobilization, functional discharge criteria and discharge to own home.

Participants: 4924 consecutive unselected unilateral primary THA and TKAs in patients ≥18 years with no preoperative use of continuous "potent" anticoagulative therapy (vitamin-K antagonists).

Exposure: Prophylaxis with low molecular weight heparin or factor Xa-inhibitors only during hospitalization when LOS ≤5 days.

Outcomes: Incidence of symptomatic TEE, VTE and VTE-related mortality ≤90 days postoperatively.

Results: LOS ≤5 days and prophylaxis only during hospitalization occurred in 4659 procedures (94.6% of total). Median LOS and prophylaxis duration was 2 days (interquartile range: 2-3) with 0.84% [95%CI: 0.62-1.15] TEE and 0.41% [0.26-0.64] VTE during 90-days follow-up. VTE consisted of 5 pulmonary embolisms (0.11% [0.05-0.25]) and 14 deep venous thrombosis (0.30% [0.18-0.50]). There were 4 (0.09% [0.04-0.23]) surgery-related deaths, of which 1 (0.02% [0.00-0.12]) was due to pulmonary embolism, and 6 (0.13% [0.06-0.28]) deaths of unknown causes after discharge.

Conclusions: The low incidence of TEE and VTE suggests that in-hospital prophylaxis only, is safe in unselected fast-track THA and TKA patients with LOS of ≤5 days. Thrombosis prophylaxis guidelines may need reconsideration in fast-track elective surgery.

Trial Registration: ClinicalTrials.gov: NCT01557725 Word count: 299/300

Article summary:

Article focus:

- Total hip (THA) and knee arthroplasty (TKA) are considered high risk procedures for venous thromboembolic events (VTE).
- Thrombosis prophylaxis for 14-35 days postoperatively is recommended, but previous studies have a length of stay in hospital (LOS) of 8-12 days and do not consider early mobilisation.
- We evaluated the incidence of symptomatic thromboembolic events (TEE) 90 days after fast-track THA and TKA in unselected patients with LOS ≤5 days and prophylaxis only during hospitalisation.

Key messages:

- Incidence of symptomatic TEE and VTE was comparable or lower than in studies with 14-35 days of postoperative prophylaxis.
- Thrombosis prophylaxis only during hospitalisation is safe in fast-track THA and TKA with early mobilisation and LOS ≤5 days

Strengths and Weaknesses:

- A prospective multicentre trial in a large cohort of consecutive unselected patients, with a standardized perioperative fast-track setup.
- Complete 90-days follow-up through the Danish National Patient Registry and patient files.
- Registration of TEE was based on review of patient files, any TEE not mentioned in these would not have been registered.

Introduction

Venous thromboembolic events (VTE) such as deep venous thrombosis (DVT) and pulmonary embolism (PE) are well documented risks in hospitalized patients[1]. Surgery presents an independent risk factor for such events, due to both the surgical trauma and postoperative immobilization. Consequently, guidelines for postoperative thrombosis prophylaxis have been developed in both general and orthopedic surgery.[2-4] However, the type and duration of prophylaxis following elective surgery is debatable.[5-7] In example, the American College of Chest Physicians (ACCP) recommends either mechanical prophylaxis using intermittent pneumatic compressive devices (IPCD) (Grade 1C), or pharmacological prophylaxis (Grade 1B), for up to 35 days (Grade 2B) after total hip (THA) and knee arthroplasty (TKA),[2] while the American Academy of Orthopedic Surgeons find the evidence inconclusive and duration of prophylaxis to be decided individually.[8] Much of the evidence regarding duration of thrombosis prophylaxis after orthopedic surgery is originating from large randomized clinical trials (RCT) in THA and TKA with prophylaxis of 10-35 days,[9-13] and these studies also contribute to guidelines in general surgery.[3] However, the pathophysiological mechanisms of thrombosis have not been addressed in the RCTs, which often have long length of stay (LOS) and lack focus on early mobilization, despite that early mobilization per se may reduce the need for thrombosis prophylaxis.[14]

Fast-track surgery has been developed to improve recovery by using evidence based care principles with multimodal opioid-sparing analgesia, reduction of the surgical stress-response, optimized fluid treatment, adjustment of use of drains and catheters, and early mobilization. These efforts have resulted in improved outcome following various procedures such as colonic surgery and gynecological procedures,[15] and major joint arthroplasty.[16] It has been suggested that reassessment of thromboembolic risk in elective surgery is needed due to few VTE,[5;17] and preliminary data have supported that fast-track THA and TKA may decrease risk of VTE and thereby the need for

prolonged prophylaxis.[6;18] Consequently, we designed a large prospective cohort study in unselected consecutive patients having fast-track THA or TKA, with thrombosis prophylaxis only during hospitalization when LOS was ≤5 days. We hypothesized there would be no increase in symptomatic TEE and VTE with prophylaxis only during hospitalization compared to previous data with prophylaxis of 10-35 days.

Methods:

We investigated consecutive unselected primary elective unilateral THA and TKA between February 1st 2010 and December 1st 2011 in patients ≥18 years with a Danish social security number and no prescriptions on "potent" anticoalgulative therapy (i.e. vitamin-K antagonists, dabigatran, rivaroxaban) ≤6 months preoperatively. Procedures in patients with more than 1 THA or TKA during the study period were excluded if <45 days between operations.

Five departments participated throughout the study period, with a sixth department pausing between March 2010 and April 2011. All departments had a known mean LOS of about 3-4 days, with a similar fast-track setup including mobilization on day of surgery, identical functional discharge criteria and discharge to own home.[19] Patients with preoperative use of platelet inhibitors (acetylic salicylic acid, clopidogrel, dypiridamol etc.) ceased treatment 3-5 days prior to admission and resumed treatment the day after surgery. All patients completed a preoperative questionnaire on characteristics and co-morbidity which was then entered into the Lundbeck Foundation Centre Database (LCDB)[20] (Appendix 1.). Thrombosis prophylaxis was only given during hospitalization in patients with LOS of ≤5 days. If LOS >5 days, prophylaxis was prescribed by the attending surgeon according to local guidelines. First dose of prophylaxis was given 6-8 hours after surgery and consisted of either: rivaroxaban (Xarelto, Bayer Pharma, Berlin, Germany) 10 mg/day, enoxaparin (Klexane, Sanofi-Aventis, Paris, France) 4000 I.U./day, dalteparin (Fragmin, Pfizer

Health Care, N.Y, U.S) 5000 I.U./day or fondaparinux (Arixtra, GlaxoSmithKline, London, U.K.) 2.5mg/day. No departments used IPCD. An interim analysis and a random-sample audit on treatment and data completion, were conducted and approved by the steering committee in 2011 (Appendix 2).

Preoperative data was cross-referenced with the Danish National Patient Registry (DNPR) regarding LOS and 90-days readmissions (including emergency room contacts, but excluding outpatient visits as clinical practice on treatment of TEE in Denmark includes an initial admission to hospital[21]). LOS was defined as number of postoperative nights in hospital (including transferal to other departments) till discharge to own home. DNPR registers all hospitalizations (including transferals, diagnoses and surgical procedures) at Danish hospitals, allowing information on LOS and readmissions regardless of localization. As reporting is mandatory for receiving reimbursement, complete follow-up is ensured.[22] To detect TEE during primary admission the complete medical records of patients with diagnosis codes related to TEE according to the International Classification of Diseases 10th revision, all transfers to other wards, and the discharge summary of any patients with LOS ≥5 days were investigated. In case of readmission ≤90-days, discharge files and/or patient files were investigated with regards to relation to surgery.[20] Criteria for TEE were predefined as: DVT confirmed by ultrasound, PE confirmed by spiral-CT, ventilation-perfusion scintigraphy or pathological removal of embolus and MI with rise in biomarkers and ischemic symptoms, diagnostic electrocardiogram changes, primary coronary intervention or coronary bypass graft. Ischemic stroke was defined as neurological symptoms >24 hours and a positive CT-scan, and transient ischemic attack (TIA) as neurological symptoms lasting less than 24 hours and no new changes on CT-scan. Mortality was obtained through the Central Office of Civil Registration using unique Danish social security numbers. Cause of death was obtained from the patient files/autopsies. In case of death outside hospital with no autopsy, the patient's general practitioner

was contacted regarding cause of death. Adjudication of discharge summaries and patient files, apart from reasons for LOS ≥5 days and death during admission, was blinded with regards to duration of thrombosis prophylaxis. Adjudication was done by the first author (CJ), and in case of possible TEE the first author (CJ) and senior author (HK) adjudicated cases together.

All prescriptions on "potent" anticoagulative therapy and platelet inhibitors 6 months before and 3 months after surgery were investigated using The Danish National Database of Reimbursed Prescriptions (DNDRP). During the study period all prescriptions on "potent" anticoagulative treatment received government reimbursements securing 100% completeness of data.[23] Patients without prescriptions on anticoagulative therapy, but answering "yes" in the questionnaire were assumed to use platelet inhibitors. In 21 procedures in patients with LOS ≤5 days we found only postoperative prescriptions on "potent" anticoagulative therapy. All hospital contacts of these patients were reviewed and, if insufficient for determining the cause of the prescription, we contacted their general practitioner. In 2 cases the prescription was due to DVT found during outpatient visits without regular hospital admission, while 7 cases were due to perioperative atrial-flutter with treatment initiated ≥22 days after discharge. These were all retained in the study cohort. The remaining 12 cases were due to specific surgical considerations, discharge from other wards or readmission with treatment despite unverified VTE. These were considered protocol violations and included in the secondary cohort.

Outcomes

Primary outcome was occurrence of symptomatic TEE (DVT, PE, arterial embolism (AE), MI, ischaemic stroke or TCA) and VTE (DVT or PE) 90 days after THA/TKA in patients with prophylaxis only during admission.

Secondary outcome was occurrence of the primary outcome in patients with thrombosis prophylaxis after discharge. Bleeding-events was protocolled as a safety endpoint, but was hindered by

incomplete registration. A separate analysis on patients not in the LCDB was done to identify potential bias.

Statistics and power calculation

A pre-study power analysis using a two-tailed one sample difference from constant test, found that 2838 patients were needed to detect a 1% increase in TEE when assuming a TEE rate of 3%, β: 82 and α: 0.05. Correspondingly, 2076 patients were needed to detect a 1% increase in symptomatic VTE assuming a 90-days baseline risk of 2%.[2]

Data were tested for normality using q-q plots and histograms. Comparisons of continuous data were made using Mann-Whitney U-test and t-test and for categorical data with χ^2-test or Fishers exact-test, as appropriate. Events (incident cases) are reported as actual number and percentage with 95% confidence intervals (95%CI) using http://www.vassarstats.net/prop1.html. All other analysis was done in SPSS v. 20 (IBM Corporation, Armonk, NY)

Results

Primary outcome

Of a total of 4924 included procedures, 4659 (94.6%) procedures in 4455 patients had LOS ≤5 days and comprised the study population (figure 1). Mean age was 66.8 years (SD:10.7) with a median LOS and prophylaxis duration of 2 days (interquartile range (IQR): 2-3) and 353 (7.6%) surgery-related readmissions (table 1).

A total of 39 (0.84%) TEE were found within 90 days, of which 24 (0.52% 95%CI: 0.35-0.77) occurred during the first postoperative month. One patient was readmitted twice due to ischemic strokes on postoperative day 8 and 46. According to the medical records, the second stroke was cardiac in origin as the patient was known with atrial flutter, but treated only with acetylsalicylic acid due to gastrointestinal bleeding. There were 19 (0.41%) symptomatic VTE (figure 2 and 3a),

consisting of 5 (0.11%) PEs and 14 (0.30%) DVTs of which 9 were proximal (table 2). Median time to VTE was 21 days (IQR: 8-39), with 12 VTE ≤30 days postoperatively (30-day VTE-rate: 0.26% 95%CI: 0.15-0.45).

There were 13 (0.28%) deaths during follow-up. Of these 3 (0.06%) were unrelated to surgery (cancer and gastric morbidity >45 days after surgery) and 6 (0.13%) were of unknown causes outside hospital (postoperative day: 19,27,36,44,48, and 85). Thus, 4 (0.09%) deaths were confirmed surgically related (table 2), 1 due to an autopsy confirmed PE on postoperative day 41 and 1 due to intracerebral bleeding on day 26. The remaining 2 deaths were due to paralytic ileus on postoperative day 36 and sepsis on postoperative day 24.

Secondary outcome

This cohort of 265 (5.4%) procedures in 263 patients (figure 1), was older and with more co-morbidity than the study cohort (table 1). Median LOS was 7 days (IQR: 6-9) with 47 (17.7%) surgically-related readmissions. Of 11 (4.97%) TEE with 7 (2.65%) VTE (table 2), 7 and 4, respectively, occurred during index hospitalization consequently resulting in LOS >5 days. Thus, the total occurrence of symptomatic in-hospital TEE and VTE during primary admission in the complete material of 4924 procedures from the LCDB was 0.14% (0.07-0.29) and 0.08% (0.03-0.21) respectively.

Of the 4 (1.51% [95%CI: 0.59-3.82]) TEE after discharge in the secondary cohort 1 (0.38% [0.07-2.11]) was an ischemic stroke and 3 were VTE (1.13% [0.38-3.27]), with 2 PEs (0.75% [0.21-2.70]) and 1 DVT (0.38% [0.07-2.11]). Median time to VTE was 3 days (IQR: 2-53) (figure 3b) in the secondary cohort. We found 3 (1.13%) surgically-related deaths, 1 death unrelated to surgery (paralytic ileus on day 70 in a patient refusing treatment) and no VTE-related deaths or deaths of unknown causes (0.00% [0.00-1.43]).

Patients not in LCDB (3.6%)

In these 194 (108 THA/86 TKA) procedures in 191 patients, mean age was 68.5 years (SD: 11.0) and 178 (91.8%) had LOS ≤5 days. In these 178 procedures there was 1 (0.56% [0.10-3.11]) readmission due to an MI, no VTE and no deaths. No further analysis was done as no bias was apparent compared to the study population.

Discussion

In this prospective study in fast-track primary THAs and TKAs with LOS ≤5 days and in-hospital thrombosis prophylaxis only, we found 90-days postoperative rates of symptomatic TEE and VTE of 0.84% and 0.41%, respectively. The patients receiving prophylaxis only during index hospitalization (median 2 days) contributed 94.6% of the total number of performed procedures, as 5.4% had LOS >5 days and consequently received longer prophylaxis. The study has several strengths, such as a consecutive unselected population including high-risk patients with various types of co-morbidity, a standardized perioperative fast-track setup, and complete detailed 90-days follow-up.

We used any TEE as primary endpoint in order not to overlook a potential worsened outcome. Stroke and MI have been included as safety endpoints in most RCTs[10-12], but are often neglected in reviews and database studies.[24-26] We found no increase in occurrence of ischemic stroke when comparing with previous in-hospital occurrences in THA[27] or with 30 day incidences in both TKA and THA[28], despite our follow-up being 90 days and not only relying on diagnostic codes. Neither was there any apparent increase in the occurrence of MI compared to a recent study which found MI in 0.51% of THA and 0.21% of TKA after 6 weeks.[29] The number of symptomatic VTE was lower or comparable to the RCTs with prophylaxis of 10 to 35 days.[10-13] However, LOS in these RCTs was 8-12 days with unspecified discharge locations, whereas LOS after 94.6% of procedures

in our study was ≤5 days until discharge to own home. The long LOS in these studies may include partial immobilization, thereby increasing the risk of VTE and consequently the need for thrombosis prophylaxis. Correspondingly, a previous small-scale study in 247 TKA found a decreased risk of DVT following mobilization within 24 hours of surgery,[14] and an earlier fast-track single-centre study with prophylaxis only during admission in 1977 THA and TKAs with a mean LOS of about 3.5 days found 0.86% symptomatic VTE within 90 days.[18]

Another main difference between our study and the RCTs is that our patients were unselected, with duration of prophylaxis depending only on discharge within 5 days, regardless of co-morbidity. Thus, our results reflect "everyday patients", whereas the exclusion criteria in the RCTs may have reduced occurrences of TEE.[8;30] The only excluded patients in our study were those using preoperative "potent" anticoagulative therapy, since they obviously needed continuation after discharge. Two Danish nationwide studies found symptomatic VTE in >1% of THA and TKA despite prolonged prophylaxis, and that the incidence was increasing across the study periods (1995-2007).[25;31] The difference between these data and ours may be due to the fast-track set-up including early mobilization in our study, and since LOS in Denmark was about 11 days in year 2000.[32]

The occurrence of in-hospital TEE in the total 4924 procedures in the LCDB was low (0.14%), and particularly the incidence of symptomatic in-hospital VTE (<0.10%) was lower than the 0.5% in THA and 1.0% in TKA found in a recent review.[24] Although the timing of VTE with the majority occurring within the first month is consistent with previous studies,[2;33] we believe that the low incidence questions the benefits of prolonged prophylaxis in all patients after fast-track THA and TKA. Further studies are needed to identify whether certain patient subgroups may benefit from more extensive or intensive prophylaxis, and how to avoid in-hospital TEE while patients are

receiving recommended treatment. However, due to the few events the numbers of patients needed for such studies pose major challenges.

Finally, we report both confirmed VTE-related death and a "worst case" scenario, with death of unknown causes being considered VTE-related, despite that cause of death after THA/TKA often is found unrelated to VTE.[34] Thus, we found only one verified fatal PE, and 90-days all-cause mortality comparable or lower than previous studies.[26;35-37]

The secondary cohort with LOS >5 days was older with more co-morbidity and readmissions. This is not surprising, as we have previously found an association with LOS and readmissions after fast-track THA and TKA in such patients.[20] There were about 2% PEs in these patients, but this is in accordance with co-morbidities such as cardiac disease or previous TEE, being associated with cardiac and thromboembolic complications after arthroplasty.[26] Furthermore, complications per se may lead to prolonged LOS and thereby longer prophylaxis. Thus, about 60% of TEE and VTE in this cohort occurred during primary admission. However, it does not argue against our conclusion that prophylaxis only during admission is safe when LOS ≤5 days.

Our study has limitations, foremost regarding the follow-up which was based on hospital contacts. However, DNPR records all readmissions independent of site of index operation, and we investigated these through discharge summaries and patient files instead of relying only on diagnostic codes, as often done in large-scale cohort studies.[25;31;38] Although TEE may have been left out of the discharge summary, this seems unlikely, as they require treatment after discharge. We also used the DNDRP to detect procedures followed by a postoperative prescription of potent antocoagulative therapy, thereby finding any TEE diagnosed in outpatient clinics. The DNDRP is ideally suited for this, as all prescriptions on oral anticoagulatives in Denmark receive reimbursement and are therefore recorded. Regarding TEE during primary admission, ideally we should have investigated the discharge summaries of every procedure with LOS ≤5 days. However,

as TEE are serious complications they would require prolonged hospitalization. Thus, LOS in all 7 patients with TEE during primary admission was >5 days (fig. 3b).

The local guidelines for thrombosis prophylaxis in the participating departments was 6-10 days after discharge when LOS >5 days, and therefore it may be problematic that we do not have exact data on duration of prophylaxis for the secondary cohort. However, this does not change the conclusion; that prophylaxis only during admission is safe in THA and TKA with LOS ≤5 days. It could also be argued that our study should have been carried out as a RCT. However we did not attempt to compare 2 types of treatment. Instead, for complex medical situations detailed cohort studies have been proposed as a viable, and sometimes preferable, alternative.[39;40] In this context, a post-hoc analysis assuming a 2% baseline risk of symptomatic VTE with extended LMWH prophylaxis of about 35 days[2] found the actual power of our study to be 99% due the large number of patients. Whether our cut-off of 5 days LOS is an optimal way of deciding on duration of prophylaxis is uncertain, but it seems unlikely that patients with a satisfactory fast-track procedure would have longer LOS.[32;36] However, it is worth noticing that >75% of procedures were followed by LOS, and consequently thrombosis prophylaxis, for ≤3 days and that about 95% of all procedures had LOS ≤5 days.

In conclusion, we found low rates of TEE and VTE after primary elective fast-track THA and TKA with thrombosis prophylaxis only during hospitalization in unselected patients with LOS ≤5 days. These results support previous findings from other types of surgery, suggesting that guidelines on postoperative thrombosis prophylaxis need reconsideration in modern elective surgical procedures.

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Contributions: CCJ updated the initial protocol, registered the trial, undertook all data gathering, performed all statistical analyses, produced all tables and figure, wrote the first manuscript draft, revised it and submitted it for publication. MKJ wrote the initial protocol, helped implement the study setup and helped revise the manuscript. KS supervised the initial protocol, implemented the study setup at Aarhus hospital, conducted the interim analysis and randomized sample audit and helped revising the manuscript. TBH helped develop the initial protocol, implemented the study setup at regional hospital Holstebro, conducted the randomised sample audit and helped revising the manuscript. HK supervised the initial protocol, supervised the work done by CCJ, contributed to data analysis and helped to draft and revise the manuscript. HH, PKA, LTH, and MBL helped develop the initial protocol, implemented the study setup at their respective study locations and revised the manuscript. All authors approved of the final version to be published. CCJ had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

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Conflicts of interests: HH and HK are board members of the Health Care initiatives, Biomet Rapid Recovery. The remaining authors declare no potential conflicts of interest.

Ethics: The Regional Ethics Committee waived the need for study approval. Permission was acquired from the Danish National Board of Health j.nr:3-3013-56/1/HKR and the Danish Data Protection Agency j.nr: 2007-58-0015 to review and store patient records without informed consent.

Trial registration: The study was registered on ClinicalTrials.gov ID: NCT01557725 prior to acquisition and analysis of data.

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Legends:

Figure 1.

Flowchart of the study population. THA: total hip arthroplasty TKA: total knee arthroplasty

Figure 2

Cumulated incidence of symptomatic venous thromboembolic events

Figure 3a and 3b

Timing of type of thromboembolic events in the study cohort (3a) and the secondary cohort (3b) TEE: thromboembolic event VTE: venous thromboembolic event. Dotted line marks postoperative day 30.

Table 1.
Preoperative patient characteristics and prophylaxis duration

Characteristic	Study cohort N: 4659	Secondary cohort N: 265	P	Characteristic	Study cohort N: 4659	Secondary cohort N: 265	P
Age (SD)	66.8 (10.7)	73.0 (12.1)	<0.001	BMI (SD)	28.4 (5.1)	27.9 (5.7)	0.110
<50	313 (6.7)	11 (4.2)		<18.5	35 (0.8)	5 (1.9)	
50-60	855 (18.4)	28 (10.6)		18.5-24.9	1186 (25.6)	79 (30.4)	
61-65	779 (16.7)	19 (7.2)		25.0-29.9	1865 (40.2)	102 (39.2)	
66-70	916 (19.7)	34 (12.8)		30.0-39.9	1426 (30.7)	63 (26.0)	
71-75	807 (17.3)	47 (17.7)		≥40	126 (2.7)	11 (3.7)	
76-80	585 (12.6)	50 (18.9)		missing	21 (0.5)	5 (1.9)	
81-86	302 (6.5)	45 (17.0)					
>86	102 (2.2)	31 (11.7)					
Gender			0.002	Joint			0.961
Females	2654 (57.0)	177 (66.8)		THA	2451 (52.6)	139 (52.5)	
Males	2005 (43.0)	88 (33.2)		TKA	2208 (47.4)	126 (47.5)	
Use of compressive stockings			<0.001	Diabetes:			0.426
				T1D	14 (0.3)	2 (0.7)	
yes	250 (5.5)	35 (13.7)		T2D	505 (10.9)	30 (11.5)	
no	4267 (94.5)	220 (86.3)		none	4112 (88.8)	230 (87.8)	
missing	142 (3.0)	10 (3.8)		missing	28 (0.6)	3 (1.1)	
Social situation			<0.001	Hypertension			<0.001
living with others	3117 (66.9)	117 (44.2)		yes	2291 (49.5)	161 (61.2)	
living alone	1502 (32.2)	139 (52.5)		no	2335 (50.5)	102 (38.8)	
nursing home etc.	40 (0.9)	9 (3.4)		missing	33 (0.7)	2 (0.8)	
Use of walking aid			<0.001	Pharmacologically treated PsD			<0.001
yes	1078 (23.7)	142 (55.0)					
no	3469 (76.3)	116 (45.0)		yes	311 (6.7)	33 (12.6)	
missing	112 (2.4)	7 (2.6)		no	4308 (93.3)	228 (87.4)	
				missing	40 (0.9)	4 (1.5)	
Hypercholesterolemia			0.044	Prior cerebral stroke			<0.001
yes	1289 (28.0)	89 (33.7)					
no	3321 (72.0)	175 (66.3)		yes	250 (5.5)	29 (11.2)	
missing	49 (1.1)	1 (0.4)		no	4336 (94.5)	229 (88.8)	
				missing	73 (1.6)	7 (2.6)	
Smoking			0.058	Prior VTE			<0.001
yes	703 (15.2)	51 (19.2)		yes	179 (3.9)	22 (8.5)	
no	3908 (84.8)	209 (80.4)		no	4401 (96.1.0)	261 (91.5)	
missing	48 (1.0)	5 (1.9)		missing	79 (1.7)	6 (2.3)	
Alcohol >2 units daily			0.015	Relative with VTE			0.023
yes	345 (7.5)	9 (3.4)		yes	507 (12.2)	16 (7.1)	
no	4263 (91.5)	252 (96.6)		no	3643 (87.8)	208 (92.9.0)	
missing	51 (1.1)	4(1.5)		missing	509 (10.9)	41 (15.5)	
Pharmacologically treated PD			0.094	Anticoagulative treatment			<0.001
yes	333 (7.2)	26 (10.0)		platelet inhibitors	1284 (26.2)	120 (39.7)	
no	4286 (92.8)	264 (90.0)		none	3375 (68.9)	145 (48.0)	
missing	44 (0.9)	5 (1.9)		missing	0 (0)	0 (0)	
Pharmacologically treated CD			0.005	Duration of prophylaxis:			
yes	418 (9.1)	37 (14.4)		mean (SD)	2.5 (0.91)	N/A	

no	4175 (90.9)	220 (85.6)	median (IQR)	2 (2-3)	N/A
missing	66 (1.4)	8 (3.0)			

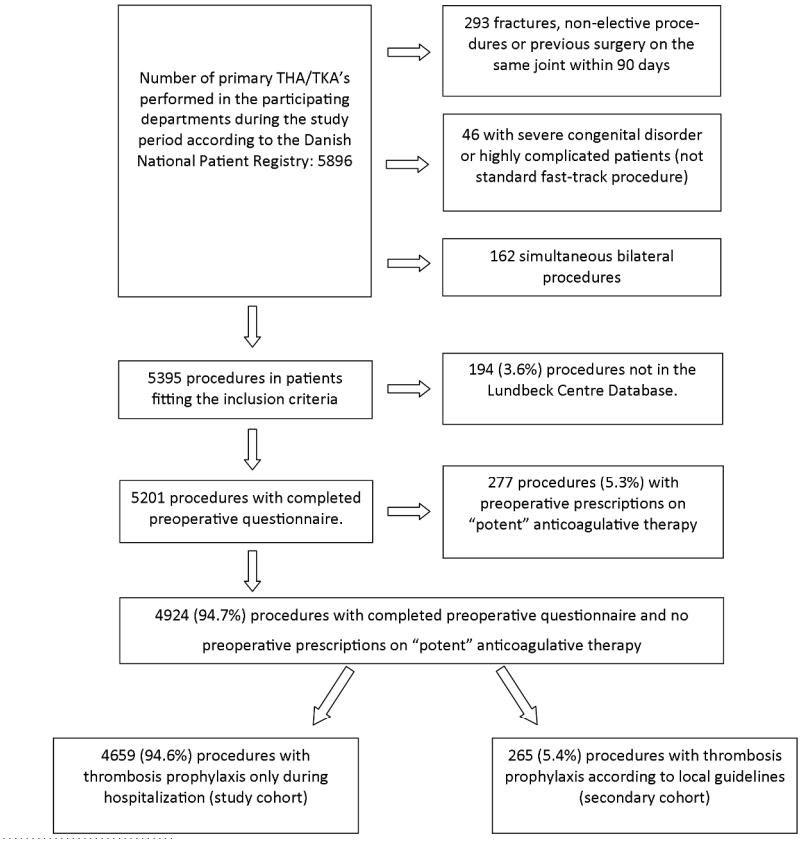
Data reported as n (%) for counts and mean for continuous variables unless otherwise specified.
N= procedures SD: Standard deviation BMI: body mass index THA: total hip arthroplasty TKA: total knee arthroplasty CD: cardiac disease T1D: type 1 diabetes T2D: type 2 diabetes PD: pulmonary disease PsD: psychiatric disease VTE: venous thromboembolic event LOS: length of hospital stay IQR: Interquartile range N/A: not available

Table 2. Venous thromboembolic events, all thromboembolic events and mortality

Outcomes	Study cohort (n:4659)	Secondary cohort (n:265)	All procedures (n:4924)
PE	5 (0.11; [0.05-0.25])	5 (1.99; [0.92-4.27])	10 (0.21; [0.12-0.38])
Any DVT	14 (0.30; [0.18-0.50])	2 (0.67; [0.18-2.38])	16 (0.37; [0.24-0.58])
Proximal DVT	9 (0.19; [0.10-0.36])	2 (0.67; [0.18-2.38])	11 (0.23; [0.13-0.41])
Any VTE	19 (0.41; [0.26-0.64])	7 (2.65; [1.35-5.14])	30 (0.58; [0.41-0.83])
Any VTE (THA/TKA)	15/4 (0.61; [0.37-1.00]) / (0.18; [0.07-0.46])	1/6 (0.65; [0.11-3.60]) / (4.70; [2.31-9.38])	17/13 (0.62; [0.39-0.99]) / (0.53; [0.31-0.90])
Myocardial infarction	7 (0.15; [0.07-0.31])	1 (0.33; [0.06-1.85])	8 (0.17; [0.09-0.32])
Ischaemic stroke	6 (0.13; [0.06-0.28])	2 (0.99; [0.34-2.87])	8 (0.19; [0.10-0.35])
Transient cerebral ischaemia	7 (0.15; [0.07-0.31])	0 (0.33; [0.06-1.85])	7 (0.15; [0.08-0.30])
Arterial embolus	0 (0.00; [0.00-0.08])	1 (0.66; [0.18-2.38])	1 (0.04; [0.01-0.14])
Any TEE	39 (0.84; [0.62-1.15])	11 (4.97; [3.04-8.04])	50 (1.12; [0.87-1.44])
Any TEE (THA/TKA)	27 /12 (1.10; [0.76-1.60]) / (0.54; [0.31-0.94])	2/9 (1.96; [0.67-5.60]) / (8.05; [4.66-13.54])	29/21 (1.17; [0.83-1.65]) / (1.05; [0.72-1.53])
All-cause mortality	13 (0.28; [0.16-0.49])	4 (1.99; [0.92-4.27])	17 (0.42; [0.28-0.64])
Unrelated to surgery	3 (0.06; [0.01-0.20])	1 (0.33; [0.06-1.85])	4 (0.10; [0.04-0.23])
Surgically related mortality	4 (0.09; [0.04-0.23])	3 (1.66; [0.71-3.82])	7 (0.19; [0.10-0.35])
Death of unknown cause	6 (0.13; [0.06-0.28])	0 (0.00; [0.00-1.26])	6 (0.13; [0.06-0.27])
Fatal PE	1 (0.02; [0.00-0.12])	0 (0.33; [0.06-1.85])	1 (0.04; [0.01-0.14])
Fatal PE/death of unknown cause	7 (0.15; [0.07-0.31])	0 (0.33; [0.06-1.85])	7 (0.17; [0.09-0.32])
Any VTE or death of unknown cause	25 (0.54; [0.37-0.80])	7 (2.65; [1.35-5.14])	32 (0.71; [0.52-0.98])
Any TEE or death of unknown cause	45 (0.97; [0.73-1.29])	11 (4.97; [3.04-8.04])	56 (1.25; [0.98-1.59])

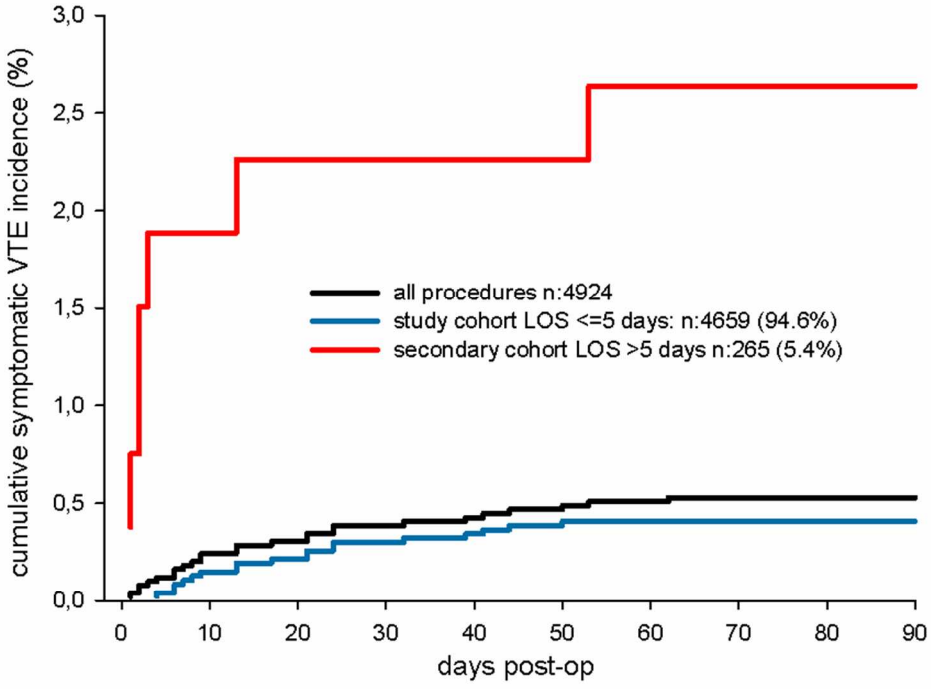
Data reported as counts n (%; [95%CI]) VTE: venous thromboembolic events TEE: thromboembolic events PE: Pulmonary embolism DVT: deep venous thrombosis THA: total hip arthroplasty TKA: total knee arthroplasty

Figure 1

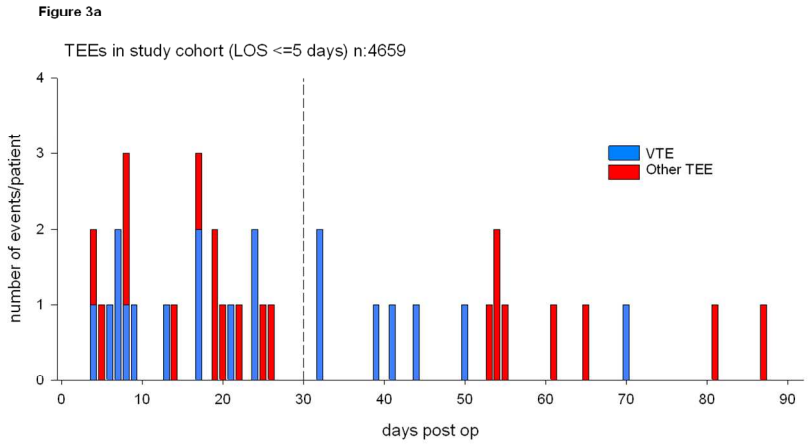


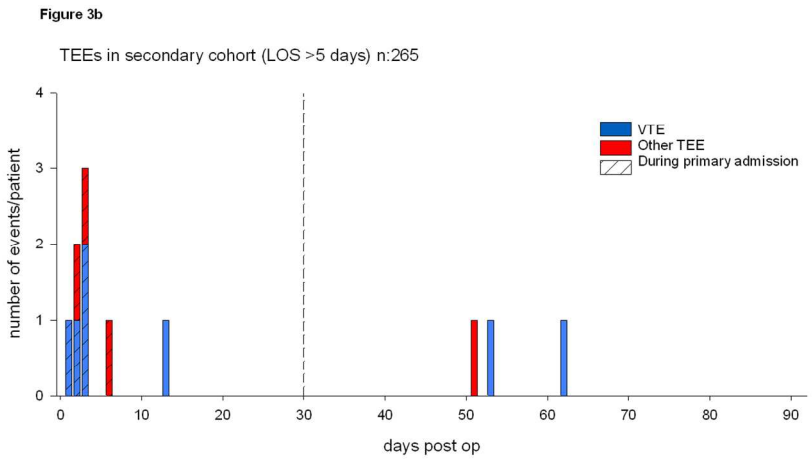
Flowchart of the study population. THA: total hip arthroplasty TKA: total knee arthroplasty
209x297mm (300 x 300 DPI)

Figure 2



Cumulated incidence of symptomatic venous thromboembolic events
154x120mm (150 x 150 DPI)





Timing of type of thromboembolic events in the study cohort (3a) and the secondary cohort (3b) TEE: thromboembolic event VTE: venous thromboembolic event. Dotted line marks postoperative day 30. 209x297mm (150 x 150 DPI)

Appendix 1

Preoperative questionnaire for the Lundbeck Centre Database

Date of surgery
Social security number

Joint (knee/hip)

Height: _____ cm
Weight: _____kg
Haemoglobin level _____ mmol/l
(Taken no more than 1 week previously)
Patients blood type?

Living conditions (alone, with spouse/others, in institution (nursing home etc.))
Smoking (yes/no)
Alcohol >2 units a day (yes/no)
Do you use walking aids prior to admission?
Are you feeling well rested in the morning?
Do you snore loudly?
Do you use compressive stockings regularly?

Do you receive treatment for high cholesterol (yes/no)
Do you receive treatment for high blood pressure (yes/no)
Do you have Type 1 diabetes (yes/no)
Do you have Type 2 diabetes (yes/no)
Have you had a previous cerebral attack?
Have you had a previous venous thromboembolic event?
Do you receive medication for any type of heart disease?
Do you receive medication for any type of pulmonary disease?
Do you receive medication for any type of psychiatric disease?
Do you have a family member who has had a deep venous thrombosis or pulmonary embolus?
Do you have a contraindication for antithrombotic medication?
Do you use antithrombotic medication regularly (courmarin, acetyl salicylic acid etc)?

Results and methods of Interim analysis and random-sample audit

Aim: To elucidate the frequency of asymptomatic deep venous thrombosis (DVT), fatal / non fatal pulmonary embolism (PE), fatal / non fatal acute myocardial infarction (AMI), stroke and transient cerebral ischemic attack (TCI) in patients undergoing elective uni- and bilateral THA /TKA, revision and uni-KA in a fast-track Set-up with short duration (3+/- 2 days) thromboprophylaxis.

Methods: Prospective multicenter study with 5000 patients. Follow-up 90 days.

Data Validation: Once collected, data are transcribed onto paper case-report forms and then entered in the database. In January 2011 a random-sample audit was performed on 250 included patients (50 patients from each center). At that time 2.622 operations were registered in the database. The purpose of the audit was a/: to ensure that included patients received short duration (3 +/-2 days) thromboprophylaxis, b/: to ensure that patients in permanent anticoagulation therapy due to previous venous thrombosis was registered, and c/: to ensure that length of stay met the fast-track criteria.

Results: All 250 patients had a completed questionnaire and no patients with LOS ≤5 days were discharged with prophylaxis except for the few (4.4%) with preoperative PACT. All departments fulfilled the fast-track criteria of mean length of hospital stay ≤3 days.

Data were compared with source documents, and checked for completeness. The result of the audit was satisfactory and approved by the steering committee.

Interim analysis: As of April 15, 2011 3.475 operations were registered in the database (1.598 knee- and 1.877 hip operations). An interim analysis was performed based on patients with complete 90 days follow-up (2.405 patients, 1.089 hips and 1.316 knees).

Table I.
Incidence of thromboembolic events (TEE) and deaths ≤90 days after 2.405 elective uni- and bilateral THA / TKA, revision and uni-KA.

	Hip surgery	Knee surgery	Total
Outcome, events pr. 1.00 [CI 99%]			
Stroke	0.09 [0.0 ; 0.6]	0.5 [1.8 ; 12.4]	0.3 [0.1 ; 0.7]
Transient cerebral ischemic attack	0.00 [0.0 ; 0.4]	0.2 [0.4 ; 7.7]	1.2 [0.02 ; 0.4]
Deep venous thrombosis	0.7 [0.3 ; 0.16]	0.5 [1.8 ; 12.4]	0.6 [0.3 ; 1.14]
Pulmonary embolism	0.2 [0.02 ; 0.8]	0.6 [2.2 ; 13.5]	0.4 [0.2 ; 0.9]
Acute myocardial infarction	0.5 [0.1 ; 1.2]	0.5 [1.4 ; 11.3]	0.5 [0.2 ;0.9]
All, events	1.4 [0.7 ; 2.5]	2.0 [1.2 ; 3.1]	1.7 [1.1 ; 2.5]
Deaths	0.4 [0.1 ; 1.1]	0.4 [0.1 ; 1.0]	0.4 [0.1 ; 0.8]
All vascular events (and all deaths)	1.7 [0.9 ; 3.0]	2.3 [1.4 ; 3.5]	20.4 [1.4 ; 2.9]

Primary endpoint: There frequency of vascular events was not increased in patients undergoing elective uni- and bilateral THA / TKA in a fast-track set-up with short duration (3+/- 2 days) thromboprophylaxis (2.04%) compared with current treatment (3%)(1-6).

Safety: No major bleedings has been reported. The frequency of non-major bleedings was not increased (0.08 %) compared with current treatment (1.5 – 1.7 %)(7).

Length of stay**:** The mean length of stay varied from 2.4 nights to 3.6 nights in the participating centers.

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*F*requency of vascular *e*vents using "short treatment"*t*hrombosis prophylaxis after fast-track hip and knee *a*rthroplasty

FETA-study

Version 3, 23/03-2012

Christoffer Calov Jørgensen, MD.

*F*requency of vascular *e*vents using "short treatment" *t*hrombosis prophylaxis in fast-track hip and knee *a*rthroplasty (FETA-study)

A prospective descriptive cohort study using prophylaxis for 3±2 days in patients receiving fast-track elective hip or knee arthroplasty

In cooperation with the Lundbeck Foundation Centre for Fast-track Hip and Knee Replacement(LCFHK).

Project leader and coordinating investigator:

Christoffer C. Jørgensen, MD/Research Fellow, Section for Surgical Pathophysiology 4074, The Juliane Marie Centre, Rigshospitalet, Blegdamsvej 9,2200 CPH Phone:+45 35454616

Clinical responsibility:

Kjeld Søballe, MD, Professor, DMSci, Department of Orthopedics, Århus University Hospital, Tage Hansens Gade

Henrik Kehlet, MD, Professor, Phd. Section for Surgical Pathophysiology 4074, The Juliane Marie Centre, Rigshospitalet, Copenhagen

Other investigators:

Per Kjærsgaard-Andersen MD, Sygehus Lillebælt

Torben Bæk Hansen MD, Professor, Regionshospitalet Holstebro

Henrik Husted, MD, Hvidovre Hospital

Lars-Peter Jorn, MD, Regionshospitalet Viborg

Mogens Berg Laursen, MD, Ortopædkirurgien Nordjylland

Lars Tambour Hansen, MD, Sydvestjysk Hospital Grindsted/Esbjerg

Statistics:

Christoffer C. Jørgensen, external statistical assistance can be requested if necessary.

Study sites:

Orthopedic departments: Århus University Hospital THG, Hvidovre Hospital, Ortopædkirurgien Nordjylland (Farsø), Regionshospitalet Holstebro, Sygehus Lillebælt, Regionshospitalet Viborg and Sydvestjysk Sygehus Grindsted/Esbjerg.

Background:

Surgery is recognized as being related to the development of thrombosis, especially after major orthopedic surgery (1;2). These complications are defined as venous thromboembolic events (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE).

Pharmacological prophylaxis reduces the risk of thrombosis and recommendations (grade 1a)from the American College of Chest Physicians (ACCP) are one of three following anticoagulantia:

1: Low molecular weight heparin (LMWH)
2: Faktor Xa-inhibitors
3: Vitamin-K-antagonists
Recommended duration of thrombosis prophylaxis is 10 days after total knee arthroplasty (TKA) and 35 days after total hip arthroplasty (THA) (3).

In the United States of America most surgeons follow ACCP guidelines. Studies have shown that about 90 % of surgeons adhere to guidelines, however, many use additional prophylaxis such as compressive stockings(4). More recent investigations find a lower compliance amongst surgeons world wide of about 50% (5). There are disagreements about the validity of the before mentioned guidelines due tothe many exclusion and inclusion criteria in the analyzed studies and due to the fact that it is the thoracic surgeons who dictate the orthopedic surgeons guidelines(6), therefore the American Academy of Orthopedic Surgeons (AAOS has developed their own guidelines. The main difference between ACCP and AAOS guidelines is the use of compressive stocking and acetylsalicylic acid as only prophylaxis in patients at risk of bleeding and a general disagreement on the relationship of DVT and PE(7).
In Denmark, the Danish Society of Orthopedic Surgeons (DSOS) has their own guidelines of 7 days of postoperative thrombosis prophylaxis which illustrates the controversies in this area.

The few studies who do not comply with ACCP guidelines, using acetylsalicylic acid (and early mobilization) as only prophylaxis show very low frequencies of vascular events (8-11), raising doubts about the best choice of treatment, especially considering increased mortality with LMWH compared to acetylsalicylic acid(12).

Preliminary uncontrolled studies in TKA have shown that early mobilization (<24 hours after surgery) reduces risk of postoperative VTE in patients treated with LMWH(13), and as frequency of DVT following TKA is decreasing over time using warfarin (VKA) as prophylaxis(14), interest in postoperative mobilization is increasing.

The trend towards enhanced recovery protocols (fast-track surgery) where optimized pain treatment, early mobilization (<24 hours), preoperative patient information etc. aims to decrease length of hospital stay. Data on THA and TKA patients from Hvidovre Hospital proves that 92 % of patients were discharged within 5 days and 41 % within 3days(15).

An un-published preliminary study from Hvidovre Hospital in about 2000 patients shows very low frequency of symptomatic VTE in 90-days follow-up, with mortality of 0.15%, DVT/PE/death in TKA of 0.66%

and 0.52% in THA when using a fast-track setup (16). This is lower than comparable literature with thrombosis prophylaxis for 35 days postoperatively.

A group of experts has suggested that pharmacological thrombosis prophylaxis in patients with early mobilization is non-obligatory, this would result in decreased side-effects such as bleedings, less inconvenience in the patients and economical advantages(17). This has resulted in short prophylaxis treatment being standard of care in several departments in Denmark (i.e. Hørsholm, Hvidovre and Farsø hospitals).

No previous study has been published with a detailed description on the risk of vascular events, including arterial complications, using short-treatment thrombosis prophylaxis in a fast-track setup after THA/TKA or commented on identification of risk factors(2;18;19).

It must be mentioned that Asian patients (Korea, China etc.) do not have a tradition for thrombosis prophylaxis after THA due to the low frequencies of VTE without prophylaxis. In this context, differences in genetics and dietary habits etc. must be considered (20;21).

1. Intention of study

1.1 Primary outcome

To conduct a high quality cohort study to investigate the frequency of symptomatic DVT, PE, acute myocardial infarction (AMI, stroke and other vascular events and/or death of other causes in patients having elective uni and bilateral THA/TKA, revision THA/TKA and uni-KA in a fast-track setup including short treatment thrombosis prophylaxis(3 ± 2 days). Additionally, identification of risk factors for such events will be attempted (Appendix 4).

1.2 Hypothesis

No increased frequency of symptomatic thromboembolic events in THA/TKA in a fast-track setup with short treatment thrombosis prophylaxis.

2. Participants and methods

2.1 Design

A detailed prospective multicenter high quality cohort study of about 5000 patients > 18 years old, having elective uni- or bilateral THA/TKA, revision and uni-KA with thrombosis prophylaxis only during hospitalization (3 ± 2 days/ 72 ± 48 hours). Follow-up is 90 days. Patients with postoperative clinical

symptoms of vascular events are encouraged to seek a physician in order to receive relevant examination and treatment (se appendix 3).

3. Patient selection

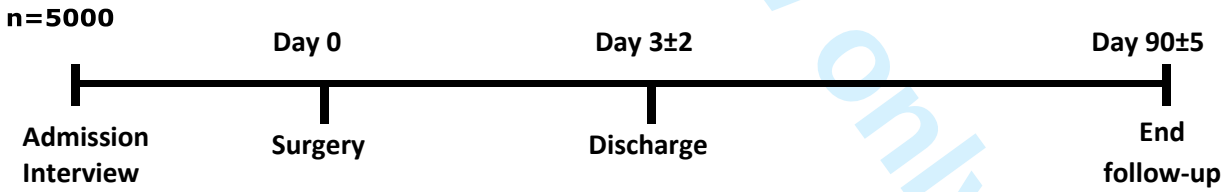
Patients will be included from the Orthopedic departments of: Århus Sygehus, Tage Hansens Gade, Regionshospitalet Holstebro, Hvidovre Hospital, Sydvestjysk sygehus Grindsted, Vejle Hospital and Ortopædkirurgien Nordjylland (Farsø), starting ultimo December ´09 til December ´11, 5000 patients need to be included. In all centers mean length of hospital stay (LOS) is short, with discharge before day 3 ± 2**.** LOS is defined as number of nights spent in hospital after surgery.

3.1 Inclusion criteria

- Males and females> 18 years old
- Primary uni/bilateral THA/TKA, revision THA/TKA and uni-KA in fast-track setup
- Discharge on day 3 ± 2/72 ± 48 hours

Observations and tests

3.2 Plan:



Day -7 til -1:

The patient goes through physical examination and demographics are registered (appendix 4).

Dag 0: defined as day of surgery

Patient has surgery

Thrombosis prophylaxis according to local guidelines (appendix 1).

Dag 3 ± **2:** Patient is discharged (4.3) and ceases thrombosis prophylaxis.

Dag 90 ± 5:End follow-up

3.3 Discharge criteria

- Independent in daily activities
- In/out of bed
- In/out of chair
- Independent walk with mobility aid

If the patient is not discharged on day 3 ± 2,the patient should follow Danish Society of Orthopedic Surgeons (DSOS) guidelines (7 days). This group will be followed separately.

In case of regular treatment with acetylsalicylic acid or other thrombocyte inhibitor, this should be continued after surgery and with addition of thrombosisprophylaxis during hospitalization.

If the patient is in regular potent anticoagulative therapy (PACT), the patient will need bridging, with cessation of PACT 4 days preoperatively, and postoperative thrombosis prophylaxis until the patient's INR reaches therapeutic values (INR 2-3). This is done by the patients' general practitioner.

4. Statistics

A pre-study power-calculation showed that at least 3000 patients were needed (power(β) 82 % with a significance level (α) of 0,05) with expected event-rates of 3% (22-25)and a maximum event rate of 4 %. We expect to include about 5000 patients which would increase power and the statistic possibility of identifying risk-factors (preoperative variables). In addition isolated analysis on the primary procedures will be performed.

5. Budget

The study is partly financed by Århus University (1.100.000dkr)and the Lundbeck Foundation Centre for Fast-track Hip and Knee Replacement(LCFHK) (550.000dkr). This has already been agreed upon.

Further project nurses/secretaries will be hired by LCFHK, therefore no further administrative assistance in relation to the project is expected.

There will be no pharmacological expenses.

Expenses in relation to transportation, travelling and course activities are expected to amount to about 50.000 dkr.

Data from the Danish National Patient Registry (NPR) about 15.000 dkr.

Other materials 5.000 dkr.

6. Safety analysis

To evaluate the risk of bleeding-complications in patients having THA or TKA in a fast-track setup (Appendix 2).

7. Duration of study

The expected duration of the study, assuming the aforementioned number of participants, is 24 months. All included patients will after 90 ±5 days be investigated by NPR. Duration of enrollment is estimated to be about 20 months. The study is expected to run from ultimo December ´09 until December ´11.

8. Interimanalysis

An interim analysis will be done after 1500 and 3000 patients.

Intention: To evaluate whether the true risk of complications is higher (worse treatment) or lower (better treatment) 4%. Three analyses will be done. In each analysis, the risk of complication including CI will be calculated. In the 1st analysis (1500 patients),the exact 99.5% CI will be calculated, in the 2nd analysis an exact 99 % CI and in the 3rd analysis (5000 pt) an exact 95.2% CI.

In simulation, it has been calculated that if the true risk is 3%, the total power is 97.6%. If the true risk of events is 6%, total power is 99.9%.

In case of an unacceptable safety profile and/or a very high number of primary events, the Clinical event committee can recommend an early termination of the study to the Steering committee, who will decide hereafter.

9. Data collection

After follow-up, data will be extracted from NPR with regards to diagnosis codes of vascular events, bleeding episodes, LOS and death. In case of events, the patient's medical charts will be requested and evaluated. The study is approved by the Danish Data Protection Agency.

10.Authors

According to alphabetical order, however, with writer as primary author and Henrik Kehlet as senior author. (13.1)

11.Study committees

The LCFHK will lead the logistic coordination of the different study committees.

11.1 Steering committee

The steering committee will ensure that all aspects of the study, such as safety and efficiency are maintained and that information from other committees can lead to timely changes.

Members:

Per Kjærsgaard-Andersen, Vejle Hospital

Torben Bæk Hansen, Regionshospitalet Holstebro

Henrik Husted, Hvidovre Hospital

Henrik Kehlet, Rigshospitalet, København

Mogens Berg Laursen, Ortopædkirurgien Nordjylland

Kjeld Søballe, Århus Universitetshospital

11.2 Clinical events committee

A clinical events committee will be founded, consisting of the writer and Steen Husted, where uncertainties regarding verification of diagnosis will be discussed. (Appendices 2+3)

12.Ethics and Legal aspects

12.1 Ethic Committee (EC)

The study will be presented to the Scientific Ethics Committee (SEC) and receive approval from here. It has been preliminarily approved as a quality-control study, as Hvidovre, Hørsholm and Farsø amongst others presently use this treatment as standard of care.

13.Ethical aspects and perspectives of the study

The duration of thrombosis prophylaxis after THA and TKA is subject to debate, both nationally and internationally. The degree of thrombo prophylactic effect vs. discomfort for the patient, bleeding-related side effects and, not the least, health related expenses need to be investigated in the "real life" setup in which the patients are operated. I Denmark the Danish Society of Orthopedic Surgeons recommend 7 days of treatment as a compromise (international recommendations up to 35 days), but also allow prolonged treatment on indication (unspecified). Studies suggest that with early mobilization and an uncomplicated postoperative phase the risk of VTE is significantly decreased. Thus there is no indication of prolonged thrombosis prophylaxis with related increased risk of bleeding-related side effects in this group(16). This study with short treatment thrombosis prophylaxis in patients having THA/TKA in a fast-track setup is in accordance with highest international expertise(17). Additionally there is disagreement regarding the American guidelines, where patients receive treatment with acetylsalicylic acid only(9).

We believe that this is a very important study, as it can influence, not only orthopedic recommendations, men generally on major surgery, such as abdominal surgery, gynecology, and other major surgical specialties using a fast-track setup(26;27). We believe that literature and, not in the least clinical experience, provide the background for a study of this character. Empirically, more and more surgeons do not follow the international recommendations and create their own. The Danish Society of Orthopedic Surgeons recommend 7 days of postoperative thrombosis prophylaxis (different from international recommendations), proving the lack of agreement in this area.

The design of the study will ensure that all data and the analysis of data will be in accordance with the Helsinki Declaration as well as local laws and regulations. The investigators will at any point allow the Steering committee or representatives of the Steering committee to review documents in order to ensure this.

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15.Appendix 1

Local postoperative prophylaxis guidelines:

ÅrhusSygehus: LMWH (Arixtra) for 7 daysin THA/ 5-7 daysFragminin TKA.

Holstebro: LMWH (Fragmin) in 7 daysin THA/TKA.

Hvidovre: X_{10a} (Xarelto) 10 mg to discharge in THA/TKA.

Ortopædkirurgien Nordjylland: LMWH (Fragmin) to discharge THA/TKA

Vejle: LMWH (Klexane) for 7 days in THA/TKA

Sydvestjysk Sygehus Grindsted: LMWH (Arixtra) 2.5mg x1 for 7 days in THA/TKA

16.Appendix 2

Bleeding

The safety endpoint is the frequency of bleeding(28)observe red no later than 2 days after last administration of thrombosis prophylaxis. Bleeding more than 2 days after last dose of thrombosis prophylaxis will not be considered as a side-effect.

Diagnosis of bleeding

In case of bleeding all information, ie. Anesthesia-charts, laboratory results, ultrasound findings, must be registered in the medical chart. All bleeding-episodes will be classified according to predefined criteria:

Serious bleeding

Minor bleedings

Serious Bleedings are:

- Fatal bleeding
- Bleeding in a critical organ(retroperitoneal, intracraniel, intraocular, intraspinal, pericardiac bleeding with tamponade, intramuscular bleeding with compartment syndrome)
- Bleeding needing surgical intervention (including joint puncture and aspiration)
- Bleeding leading to infusion of >1 portion of SAGM/full blood
- Bleeding index ≥2 (defined as number of transfused portions of erythrocytes + diff between hemoglobin before and after bleeding measured in gram/dl).
- Drop in hemoglobin of > 30g/L (=1,9mmol/L)
- **All bleedings not classified as serious bleedings will be classified as minor bleedings**

17.Appendix 3

Definition of clinical outcomes:

17.1 DVT

Diagnosis done by ultrasound (if not possible venography). The main criteria for DVT is a negative compression test with ultrasound(9).

17.2 Pulmonary embolism

Diagnosed by

- Spiral CT-scan (29)
- Perfusion-ventilation scintigrafia(9)
- Pathologicalremoval of embolus(9)

17.3 Myocardial infarction

Diagnosed in the following situations(30)

- Increase and/or fall in specific biomarkers (mainly troponin) with at least 1 value higher than the 99 percentile of upper reference threshold and

  Evidence for myocardial ischemia with at leastone of the following:

  - Symptoms of ischemia (chest pain, dyspnoea, acute heart failure, arrhythmia)

  - ECG changes indicative of acute ischemia (new ST-T changes or new left side bundle branch block)

  - Development of pathological Q-waves on ECG

  - Radiological diagnostic evidence of new loss of viable myocardium or new regional dyskinesia.

  - Revasculisation by PCI or CABG.

17.4 Stroke

Defined as an acute neurological event with focal neurologic deficits and duration beyond 24 hours (31), verified by CT/MR-scan. Strokes will be stratified according to type as ischemic, hemorrhagic or unknown.

In case of progression of formerly known neurological symptoms, the progression must be present for more than 1 week or 24 hours if accompanied by new relevant CT or MR findings.

Cardiovascular death

Death of vascular causes include cardiovascular, cerebrovascular and death of other vascular causes or death with no clear documentation of non-vascular cause. Ex:

Vascular death: Sudden death, MI, unstable angina pectoris, other CAD, stroke, arterial embolism, pulmonary embolism, dissecting aorta, heart insufficiency, cardiac arrhythmia, or death from bleeding (non-trauma related)

Non-vascular death: Respiratory failure, pneumonia, cancer, trauma, suicide or other defined cause (i.e. liver or renal failure)

Death of unknown /uncertain causes will be categorized as vascular death.

TCI

Definition is as for stroke, but are temporary and gone <24 hours.

17.5 Other thromboembolic events

Need to be defined by a relevant specialist.

18.Appendix 4

Date of surgery

Social security number

Joint (knee/hip)

Height: _____ cm

Weight: _____kg

Hemoglobin level _____ mmol/l

(Taken no more than 1 week previously)

Patients' blood type?

Living conditions (alone, with spouse/others, in institution (nursing home etc.)

Smoking (yes/no)

Alcohol >2 units a day (yes/no)

Do you use walking aids prior to admission?

Are you feeling well rested in the morning?

Do you snore loudly?

Do you use compressive stockings regularly?

Do you receive treatment for high cholesterol (yes/no)

Do you receive treatment for high blood pressure (yes/no)

Do you have Type 1 diabetes (yes/no)

Do you have Type 2 diabetes (yes/no)

Have you had a previous cerebral attack?

Have you had a previous venous thromboembolic event?

Do you receive medication for any type of heart disease?

Do you receive medication for any type of pulmonary disease?

Do you receive medication for any type of psychiatric disease?

Do you have a family member who has had a deep venous thrombosis or pulmonary embolus?

Do you have a contraindication for antithrombotic medication?

Do you use antithrombotic medication regularly (marevan, acetyl salicylic acid etc)?

19. Protocol editing and changes after study initiation

1) **Project leader and coordinating investigator:** Changed from Michael Kjær Jacobsen to Christoffer C. Jørgensen
2) **Other investigators:** The following investigators have been removed as the study was not initiated at their institutions: Steen Husted MD, Århus Universitety Hospital, THG Århus, Søren Mikkelsen MD, Regionshospitalet Silkeborg.
   The following investigators have been edited: Søren Solgaard MD, Gentofte Hospital Gentofte.
   The following investigators have been added: Lars Tambour Hansen MD, Sydvestjysk Sygehus Grindsted/Esbjerg
3) **Statistician:** Niels Trolle Andersen is no longer responsible for statistics. Christoffer C. Jørgensen has been added and additional assistance will be acquired as needed.
4) **Study sites:**The following study sites have not participated: Regionshospitalet Silkeborg, Hørsholm Hospital (due to closure). The following study sites have been added: Sydvestjysk Hospital Grindsted/Esbjerg April 2010, Gentofte Hospital, November 2012.
5) **Background:** Hørsholm Hospital has been mentioned as having used short-treatment prophylaxis as standard of care. This is a mistake and should be omitted.
6) **2.1 Design:** Due to a large number of available patients, it has been decided to expand the study size. The intention is now to include 5000 PRIMARY operations in addition to a number of revisions and uni-KA. 3.
7) **3. Patient selection:** Changes according to 4) **Study sites**.
8) **3.3 Discharge criteria:** Thrombosis prophylaxis in patients with LOS >5 days: DOS guidelines are not 7 days, but 5-10 days in TKA and 7-35 days after THA.
9) **4. Statistics:** The exact number of patients when using a Two-tailed one sample difference from constant test with the in the protocol mentioned specifications is 2838. Using the same test, 2076 patients will be needed to detect a 1% increase in frequency of symptomatic VTE, using α: 0.05, β: 82 and a baseline risk of 1% with 35 days of treatment with LMWH.
10) **7. Duration of study:** As the database of this study forms the core of several independent studies on co-morbidity, duration of this study has been extended, and database registration is expected to last until ultimo 2016
11) **9. Data collection:** Collection of data has been changed from depending on ICD-10 diagnostic codes for vascular events only to include ALL readmissions in 90 days. These will be investigated using discharge papers and complete medical charts in order to increase quality of data. In addition further details on regular anti-coagulative therapy 6 months prior to surgery and 3 months after surgery be collected through a newly established cooperation with the Danish National Database of Reimbursed Prescriptions, in order to further improve data quality.[1]
12) **10. Authors:** Christoffer Calov Jørgensen is now primary author, Michael Kjær Jacobsen will figure as secondary author and Henrik Kehlet as senior author. The remaining investigators are co-authors in a random order when patients from their study sites are included in the specific studies.
13) **11.1 Steering committee:** The following persons are not part of the steering committee: Steen Husted, Lars-Peter Jorn, Søren Mikkelsen, Søren Solgaard.
14) **11.2 Clinical event Committee:** Consists of Christoffer Calov Jørgensen and Henrik Kehlet.
15) **12.1 Ethic Committee:** The study ended up being considered as a quality-control study on a standard of care. The Scientific Ethics Committee decided that the study needed no approval.
16) **Appendix 1:** The local prophylaxis guidelines of the following departments are not relevant: Hørsholm and Silkeborg. Guidelines for the added departments are: Gentofte Hospital: X_{10a} inhibitor (Xarelto) 10 mg x 1 in both THA/TKA until discharge. Sydvestjysk Sygehus Grindsted: LMWH (Arixtra) 2.5mg x 1 for 7 days. Treatment has been changed after study initiation in the

following departments: Hvidovre Hospital: X_{10a} inhibitor (Xarelto) 10 mg to discharge THA/TKA. Viborg Hospital: LMWH (Fragmin) 5000 ie x 1 for 10 days.

[1]Johannesdottir SA, Horváth-Puhó E, Schmidt M, Ehrenstein V, Pedersen L, Sørensen HT. Existing data sources for clinical epidemiology:The Danish National Database of Reimbursed Prescriptions. *Clin Epidemiol* 2012;4:1-11.

Thromboprophylaxis only during hospitalization in fast-track hip and knee arthroplasty, a prospective cohort study

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Complete List of Authors:	Jørgensen, Christoffer; Rigshopsitalet, Copenhagen University, Section for Surgical Pathophysiology Jacobsen, Michael; Aarhus University Hospital, Department of Orthopaedics Soballe, Kjeld; Aarhus University Hospital, Aarhus University, Department of Orthopaedics Hansen, Torben; Regional Hospital Holstebro, Aarhus University, Department of Orthopaedics Husted, Henrik; Hvidovre Hospital, Copenhagen University, Orthopaedic Department Kjaersgaard-Andersen, Per; Vejle Hospital, University of Southern Denmark, Department of Orthopedics Hansen, Lars; Sydvestjysk Hospital Esbjerg/Grindsted, Orthopedic Department Laursen, Mogens; Aalborg University Hospital, Aalborg University, Northern Orthopaedic Division Kehlet, Henrik; Rigshopsitalet, Copenhagen University, Section for Surgical Pathophysiology
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Thromboprophylaxis only during hospitalization in fast-track hip and knee arthroplasty, a prospective cohort study

Christoffer C Jørgensen*, Michael K Jacobsen, Kjeld Soeballe, Torben B Hansen, Henrik Husted, Per Kjærsgaard-Andersen, Lars T Hansen, Mogens B Laursen, and Henrik Kehlet

Section for Surgical Pathophysiology 4074, The Juliane Marie Centre, Rigshospitalet, Copenhagen University, 2100 Copenhagen, Denmark Christoffer C Jørgensen Research fellow

Department of Orthopaedics, Aarhus University Hospital, Aarhus University, Brendstrupgårdsvej 100, 8200 Aarhus N, Denmark Michael K Jacobsen Orthopaedic Surgeon

Department of Orthopaedics, Aarhus University Hospital, Aarhus University, Brendstrupgårdsvej 100, 8200 Aarhus N, Denmark Kjeld Soeballe Professor

Department of Orthopaedics, Regional Hospital Holstebro, Aarhus University, Lægårdvej 12 7500 Holstebro, Denmark Torben B Hansen Professor

Orthopaedic Department, Hvidovre University Hospital, Kettegård Alle 30, 2650 Hvidovre, Denmark Henrik Husted Senior Consultant

Department of Orthopedics, Vejle Hospital, University of Southern Denmark, Kabbeltoft 25, 7100 Vejle, Denmark Per Kjærsgaard-Andersen Associate Professor

Orthopaedic Department, Sydvestjysk Hospital Esbjerg/Grindsted, Engparken 1, 7200 Grindsted, Denmark Lars T Hansen Senior Consultant

Aalborg University Hospital Northern Orthopaedic Division, Aalborg University, Højgårdsvej 11, 9640 Farsø, Denmark Mogens B Laursen Associate Professor

Section for Surgical Pathophysiology 4074, The Juliane Marie Centre, Rigshospitalet, Copenhagen University, 2100 Copenhagen, Denmark Henrik Kehlet Professor

All authors are members of The Lundbeck Foundation Centre for Fast-track Hip and Knee Replacement 2100 Copenhagen, Denmark.

*Corresponding author: christoffer.calov.joergensen@regionh.dk Section for Surgical Pathophysiology 4074, The Juliane Marie Centre, Rigshospitalet, Copenhagen University, 2100 Copenhagen, Denmark

Trial Registration: ClinicalTrials.gov: NCT01557725 Word count: 299/300

Abstract:

Objectives: International guidelines recommend thrombosis prophylaxis after total hip (THA) and knee arthroplasty (TKA) for up to 35 days. However previous studies often have hospital stays (LOS) of 8-12 days and not considering early mobilisation, which may reduce incidence of venous thromboembolic events (VTE). We investigated the incidence of any symptomatic thromboembolic events (TEE) with only in-hospital prophylaxis if LOS ≤5 days after fast-track THA and TKA.

Design: A prospective descriptive multicenter cohort study in fast-track THA and TKA from February 2010 to December 2011, with complete 90-days follow-up through the Danish National Patient Registry and patient files.

Setting: 6 Danish high-volume centers with a similar standardized fast-track setup, including spinal anaesthesia, opioid-sparing analgesia, early mobilization, functional discharge criteria and discharge to own home.

Participants: 4924 consecutive unselected unilateral primary THA and TKAs in patients ≥18 years with no preoperative use of continuous "potent" anticoagulative therapy (vitamin-K antagonists).

Exposure: Prophylaxis with low molecular weight heparin or factor Xa-inhibitors only during hospitalization when LOS ≤5 days.

Outcomes: Incidence of symptomatic TEE, VTE and VTE-related mortality ≤90 days postoperatively.

Results: LOS ≤5 days and thromboprophylaxis only during hospitalization occurred in 4659 procedures (94.6% of total). Median LOS and prophylaxis duration was 2 days (interquartile range: 2-3) with 0.84% [95%CI: 0.62-1.15] TEE and 0.41% [0.26-0.64] VTE during 90-days follow-up. VTE consisted of 5 pulmonary embolisms (0.11% [0.05-0.25]) and 14 deep venous thrombosis (0.30% [0.18-0.50]). There were 4 (0.09% [0.04-0.23]) surgery-related deaths, of which 1 (0.02% [0.00-0.12]) was due to pulmonary embolism, and 6 (0.13% [0.06-0.28]) deaths of unknown causes after discharge.

Conclusions: The low incidence of TEE and VTE suggests that in-hospital prophylaxis only, is safe in fast-track THA and TKA patients with LOS of ≤5 days. Guidelines on thromboprophylaxis may need reconsideration in fast-track elective surgery.

Trial Registration: ClinicalTrials.gov: NCT01557725

Article summary:

Article focus:

- Total hip (THA) and knee arthroplasty (TKA) are considered high risk procedures for venous thromboembolic events (VTE).
- Thromboprophylaxis for 14-35 days postoperatively is recommended, but previous studies have a length of stay in hospital (LOS) of 8-12 days and do not consider early mobilisation.
- We evaluated the incidence of symptomatic thromboembolic events (TEE) 90 days after fast-track THA and TKA in patients with LOS ≤5 days and thromboprophylaxis only during hospitalisation.

Key messages:

- Incidence of symptomatic TEE and VTE was comparable or lower than in studies with 14-35 days of postoperative thromboprophylaxis.
- Thromboprophylaxis only during hospitalisation is safe in fast-track THA and TKA with early mobilisation and LOS ≤5 days

Strengths and Weaknesses:

- A prospective multicentre trial in a large cohort of consecutive unselected patients, with a standardized perioperative fast-track setup.
- Complete 90-days follow-up through the Danish National Patient Registry and patient files.

- Registration of TEE was based on review of patient files, any TEE not mentioned in these would not have been registered.

Introduction

Venous thromboembolic events (VTE) such as deep venous thrombosis (DVT) and pulmonary embolism (PE) are well documented risks in hospitalized patients[1]. Surgery presents an independent risk factor for such events, due to both the surgical trauma and postoperative immobilization. Consequently, guidelines for postoperative thromboprophylaxis have been developed in both general and orthopedic surgery.[2-4] However, the type and duration of prophylaxis following elective surgery is debatable.[5-7] For example, the American College of Chest Physicians (ACCP) recommends either mechanical prophylaxis using intermittent pneumatic compressive devices (IPCD) (Grade 1C), or pharmacological prophylaxis (Grade 1B), for up to 35 days (Grade 2B) after total hip (THA) and knee arthroplasty (TKA),[2] whereas the American Academy of Orthopedic Surgeons find the evidence inconclusive and decide the duration of thromboprophylaxis on an individual basis.[8] Much of the evidence regarding duration of thromboprophylaxis after orthopedic surgery has originated from large randomized clinical trials (RCT) in THA and TKA with prophylaxis of 10-35 days,[9-13] and these studies also contribute to guidelines in general surgery.[3] However, the pathophysiological mechanisms of thrombosis have not been addressed in the RCTs, which often have long length of stay (LOS) and lack focus on early mobilization, despite the fact that early mobilization per se may reduce the need for thromboprophylaxis.[14]

Fast-track surgery has been developed to improve recovery by using evidence based care principles with multimodal opioid-sparing analgesia, reduction of the surgical stress-response, optimized fluid treatment, adjustment of the use of drains and catheters, and early mobilization. These efforts have resulted in improved outcome following various procedures such as colonic surgery and gynaecological procedures,[15] and major joint arthroplasty.[16] It has been suggested that

reassessment of thromboembolic risk in elective surgery is needed due to few incidences of VTE,[5;17] and preliminary data have supported that fast-track THA and TKA may decrease risk of VTE and thereby the need for prolonged prophylaxis.[6;18] Consequently, we designed a large prospective cohort study in unselected consecutive patients having fast-track THA or TKA, with thromboprophylaxis only during hospitalization when LOS was ≤5 days. We hypothesized there would be no increase in symptomatic TEE and VTE with prophylaxis only during hospitalization compared to previous data with prophylaxis of 10-35 days.

Methods:

We investigated consecutive unselected primary elective unilateral THA and TKA between February 1st 2010 and December 1st 2011 in patients ≥18 years with a Danish social security number and no prescriptions on "potent" anticoagulant therapy (i.e. vitamin-K antagonists, dabigatran, rivaroxaban) ≤6 months preoperatively. Procedures in patients with more than 1 THA or TKA during the study period were excluded if <45 days between operations.

Five departments participated throughout the study period, with a sixth department pausing between March 2010 and April 2011. All departments had a known mean LOS of about 3-4 days, with a similar fast-track setup including mobilization on day of surgery, identical functional discharge criteria and discharge to own home.[19] Patients with preoperative use of platelet inhibitors (acetylic salicylic acid, clopidogrel, dypiridamol etc.) ceased treatment 3-5 days prior to admission and resumed treatment the day after surgery. All patients completed a preoperative questionnaire on characteristics and co-morbidity which was then entered into the Lundbeck Foundation Centre Database (LCDB)[20] (Appendix 1.). Thromboprophylaxis was only given during hospitalization in patients with LOS of ≤5 days. If LOS >5 days, prophylaxis was prescribed by the attending surgeon according to local guidelines. First dose of prophylaxis was given 6-8 hours after surgery and

consisted of either: rivaroxaban (Xarelto, Bayer Pharma, Berlin, Germany) 10 mg/day, enoxaparin (Klexane, Sanofi-Aventis, Paris, France) 4000 I.U./day, dalteparin (Fragmin, Pfizer Health Care, N.Y, U.S) 5000 I.U./day or fondaparinux (Arixtra, GlaxoSmithKline, London, U.K.) 2.5mg/day. No departments used IPCD. An interim analysis and a random-sample audit on treatment and data completion, were conducted and approved by the steering committee in 2011 (Appendix 2). Preoperative data was cross-referenced with the Danish National Patient Registry (DNPR) regarding LOS and 90-days readmissions (including emergency room contacts, but excluding outpatient visits as clinical practice on treatment of TEE in Denmark includes an initial admission to hospital[21]). LOS was defined as number of postoperative nights in hospital (including transferal to other departments) till discharge to the patients' own home. DNPR registers all hospitalizations (including transferals, diagnoses and surgical procedures) at Danish hospitals, allowing information on LOS and readmissions regardless of localization. Reporting is mandatory for receiving reimbursement ensuring completeness of data of about 99.4%.[22;23] To detect TEE during primary admission the complete medical records of patients with diagnosis codes related to TEE according to the International Classification of Diseases 10th revision, all transfers to other wards, and the discharge summary of any patients with LOS ≥5 days were investigated. In case of readmission ≤90-days, discharge files and/or patient files were investigated with regards to relation to surgery.[20] Criteria for TEE were predefined as: DVT confirmed by ultrasound, PE confirmed by spiral-CT, ventilation-perfusion scintigraphy or pathological removal of embolus and MI with rise in biomarkers and ischemic symptoms, diagnostic electrocardiogram changes, primary coronary intervention or coronary bypass graft. Ischemic stroke was defined as neurological symptoms >24 hours and a positive CT-scan, and transient ischemic attack (TIA) as neurological symptoms lasting less than 24 hours and no new changes on CT-scan. Mortality was obtained through the Central Office of Civil Registration using unique Danish social security numbers. Cause of death was

obtained from the patient files/autopsies. In case of death outside hospital with no autopsy, the patient's general practitioner was contacted regarding cause of death. Adjudication of discharge summaries and patient files, apart from reasons for LOS ≥5 days and death during admission, was blinded with regards to duration of thrombosis prophylaxis. Adjudication was done by the first author (CJ), and in case of possible TEE the first author (CJ) and senior author (HK) adjudicated cases together.

All prescriptions on "potent" anticoagulant therapy and platelet inhibitors 6 months before and 3 months after surgery were investigated using The Danish National Database of Reimbursed Prescriptions (DNDRP). During the study period all prescriptions on "potent" anticoagulant treatment received government reimbursements securing 100% completeness of data.[24] Patients without prescriptions on anticoagulative therapy, but answering "yes" in the questionnaire were assumed to use platelet inhibitors. In 21 procedures in patients with LOS ≤5 days we found only postoperative prescriptions on "potent" anticoagulative therapy. All hospital contacts of these patients were reviewed and, if insufficient for determining the cause of the prescription, we contacted their general practitioner. In 2 cases the prescription was due to DVT found during outpatient visits without regular hospital admission, while 7 cases were due to perioperative atrial-flutter with treatment initiated ≥22 days after discharge. These were all retained in the study cohort. The remaining 12 cases were due to specific surgical considerations, discharge from other wards or readmission with treatment despite unverified VTE. These were considered protocol violations and included in the unsuccessful early discharge cohort.

Outcomes

Primary outcome was occurrence of symptomatic TEE (DVT, PE, arterial embolism (AE), MI, ischaemic stroke or TCA) and VTE (DVT or PE) 90 days after THA/TKA in patients with prophylaxis only during admission.

Secondary outcome was occurrence of the primary outcome in patients with thromboprophylaxis after discharge. Bleeding-events were protocolled as a safety endpoint, but was hindered by incomplete registration. A separate analysis on patients not in the LCDB was done to identify potential bias.

Statistics and power calculation

A pre-study power analysis using a two-tailed one sample difference from constant test, found that 2838 patients were needed to detect a 1% increase in TEE when assuming a TEE rate of 3%, β: 82 and α: 0.05. Correspondingly, 2076 patients were needed to detect a 1% increase in symptomatic VTE assuming a 90-days baseline risk of 2%.[2]

Data were tested for normality using q-q plots and histograms. Comparisons of continuous data were made using Mann-Whitney U-test and t-test and for categorical data with χ^2-test or Fishers exact-test, as appropriate. Events (incident cases) are reported as actual number and percentage with 95% confidence intervals (95%CI) using http://www.vassarstats.net/prop1.html. All other analysis was done in SPSS v. 20 (IBM Corporation, Armonk, NY)

Results

Total cohort

A total of 4924 procedures in 4718 patients were included. Median LOS was 2 days (IQR: 2-3), and readmissions occurred after 400 (8.1%) of all procedures. We found 50 (1.12%) TEE, of which 30 (0.58%) were VTE. Symptomatic in-hospital TEE occurred after 7 (0.14% [0.07-0.29]) procedures

of which 4 (0.08% [0.03-0.21]) were VTE. All-cause mortality was 0.42%, including one fatal PE (0.04%) and 6 deaths of unknown causes (0.1%) (table 2).

Successful early discharge cohort

Early discharge with LOS ≤5 days occurred in 4659 (94.6%) procedures in 4455 patients (figure 1). These patients had a mean age of 66.8 years (SD: 10.7) with a median LOS and prophylaxis duration of 2 days (interquartile range (IQR): 2-3) (table 1). There were 353 (7.6%) surgery-related readmissions of which 2.9% were due to "surgical" morbidity (hip displacements, prosthesis infections, knee manipulation etc.) and 4.7% were due to "medical" morbidity, such as anaemia, cardiac arrhythmia, pneumonia, unverified prosthesis infection and pain.

A total of 39 (0.84%) TEE were found within 90 days, of which 24 (0.52% 95%CI: 0.35-0.77) occurred during the first postoperative month. One patient was readmitted twice due to ischemic strokes on postoperative days 8 and 46. According to the medical records, the second stroke was cardiac in origin as the patient was known with atrial flutter, but treated only with acetylsalicylic acid due to gastrointestinal bleeding. There were 19 (0.41%) symptomatic VTE (figure 2 and 3a), consisting of 5 (0.11%) PEs and 14 (0.30%) DVTs of which 9 were proximal (table 2). Median time to VTE was 21 days (IQR: 8-39), with 12 VTE ≤30 days postoperatively (30-day VTE-rate: 0.26% 95%CI: 0.15-0.45).

There were 13 (0.28%) deaths during follow-up. Of these 3 (0.06%) were unrelated to surgery (cancer and gastric morbidity >45 days after surgery) and 6 (0.13%) were of unknown causes outside hospital (postoperative day: 19,27,36,44,48, and 85). Thus, 4 (0.09%) deaths were confirmed surgically related (table 2), 1 due to an autopsy confirmed PE on postoperative day 41 and 1 due to intracerebral bleeding on day 26. The remaining 2 deaths were due to paralytic ileus on postoperative day 36 and sepsis on postoperative day 24.

The "unsuccessful" early discharge cohort This cohort of 265 (5.4%) procedures in 263 patients (figure 1), was older and had more co-morbidity than the early discharge cohort (table 1). Median LOS was 7 days (IQR: 6-9) with 47 (17.7%) surgically-related readmissions (5.7% "surgical" and 12.0% "medical" morbidity). Of 11 (4.97%) TEE with 7 (2.65%) VTE (table 2), 7 and 4, respectively, occurred during index hospitalization consequently resulting in LOS >5 days. Of the 4 (1.51% [95%CI: 0.59-3.82]) TEE after discharge, 1 (0.38% [0.07-2.11]) was an ischaemic stroke and 3 were VTE (1.13% [0.38-3.27]), with 2 PEs (0.75% [0.21-2.70]) and 1 DVT (0.38% [0.07-2.11]). Median time to VTE was 3 days (IQR: 2-53) (figure 3b). We found 3 (1.13%) surgically-related deaths, 1 death unrelated to surgery (paralytic ileus on day 70 in a patient refusing treatment) and no VTE-related deaths or deaths of unknown causes (0.00% [0.00-1.43]).

Patients not in LCDB (3.6%)

In these 194 (108 THA/86 TKA) procedures in 191 patients, mean age was 68.5 years (SD: 11.0) and 178 (91.8%) had LOS ≤5 days. In these 178 procedures there was 1 (0.56% [0.10-3.11]) readmission due to an MI, no VTE and no deaths. No further analysis was done as no bias was apparent compared to the study population.

Discussion

In this prospective study in fast-track primary THAs and TKAs, we found 90-days postoperative rates of symptomatic TEE and VTE of 0.84% and 0.41% respectively, in patients with LOS ≤5 days and in-hospital thromboprophylaxis only. The patients receiving prophylaxis only during index hospitalization (median 2 days) contributed 94.6% of the total number of performed procedures, as 5.4% had LOS >5 days and consequently received longer prophylaxis. The study has several strengths, such as a consecutive unselected population including high-risk patients with various

types of co-morbidity, a standardized perioperative fast-track setup, and complete detailed 90-days follow-up.

We used any TEE as primary endpoint in order not to overlook a potential worsened outcome. Stroke and MI have been included as safety endpoints in most RCTs[10-12], but are often neglected in reviews and database studies.[25-27] We found no increase in the occurrence of ischemic stroke compared to previous studies of in-hospital stroke in THA[28] and strokes ≤30 days in both TKA and THA,[29] despite our follow-up being 90 days and not only relying on diagnostic codes. Neither was there any apparent increase in the occurrence of MI compared to a recent study which found MI in 0.51% of THA and 0.21% of TKA after 6 weeks.[30] The numbers of symptomatic VTE were lower or comparable to the RCTs with prophylaxis of 10 to 35 days.[10-13] However, LOS in these RCTs was 8-12 days with unspecified discharge locations, whereas LOS after 94.6% of procedures in our study was ≤5 days until discharge to own home. The long LOS in these studies may include partial immobilization, thereby increasing the risk of VTE and consequently the need for thromboprophylaxis. Correspondingly, a previous small-scale study in 247 TKA found a decreased risk of DVT following mobilization within 24 hours of surgery,[14] and an earlier fast-track single-centre study with prophylaxis only during admission in 1977 THA and TKAs with a mean LOS of about 3.5 days found 0.86% symptomatic VTE within 90 days.[18]

Another main difference between our study and the RCTs is that there was no preoperative selection of patients, as duration of prophylaxis depended only on discharge within 5 days, regardless of co-morbidity. Thus, our results reflect “everyday patients”, whereas the exclusion criteria in the RCTs may have reduced occurrences of TEE.[8;31] The only excluded patients in our study were those using preoperative “potent” anticoagulant therapy, since they obviously needed continuation after discharge. Two Danish nationwide studies found symptomatic VTE in >1% of THA and TKA despite prolonged prophylaxis, and that the incidence was increasing across the

study periods (1995-2007).[26;32] The difference between these data and ours may be due to the fast-track set-up including early mobilization in our study, and since LOS in Denmark was about 11 days in year 2000.[33]

The occurrence of in-hospital TEE in the total 4924 procedures in the LCDB was low (0.14%), and particularly the incidence of symptomatic in-hospital VTE (<0.10%) was lower than the 0.5% in THA and 1.0% in TKA found in a recent review.[25] Although the timing of VTE, -with the majority occurring within the first month is consistent with previous studies,[2;34] we believe that the low incidence questions the benefits of prolonged prophylaxis in all patients after fast-track THA and TKA. Further studies are needed to identify whether certain patient subgroups may benefit from more extensive or intensive prophylaxis, and how to avoid in-hospital TEE while patients are receiving recommended treatment. However, due to the few events the numbers of patients needed for such studies pose major challenges.

Finally, we report both confirmed VTE-related death and a "worst case" scenario, with death of unknown causes being considered VTE-related, despite that cause of death after THA/TKA often is found unrelated to VTE.[35] Thus, we found only one verified fatal PE, and a 90-day all-cause mortality comparable to or lower than previous studies.[27;36-38]

The "unsuccessful" early discharge cohort was older with more co-morbidity and readmissions. This is not surprising, as we have previously found an association with LOS and readmissions after fast-track THA and TKA in such patients.[20] There were about 2% PEs in these patients, but this is in accordance with co-morbidities such as cardiac disease or previous TEE, being associated with cardiac and thromboembolic complications after arthroplasty.[27] Furthermore, complications per se may lead to prolonged LOS and thereby longer prophylaxis. Thus, about 60% of TEE and VTE in this cohort occurred during primary admission. However, it does not argue against our conclusion that prophylaxis only during admission is safe when LOS ≤5 days.

Our study has limitations, foremost regarding the follow-up which was based on hospital contacts. However, although the reliability of diagnostic codes for VTE in DNPR may be low,[39] completion of data regarding somatic admissions is close to 100% .[22;39] Consequently, we investigated all admissions through discharge summaries and patient files instead of relying only on diagnostic codes, as often done in large-scale cohort studies.[26;32;40] Although TEE may have been left out of the discharge summary, this seems unlikely, as they require treatment after discharge. We also used the DNDRP to detect procedures followed by a postoperative prescription of potent anticoagulant therapy, thereby ensuring that any TEE diagnosed in outpatient clinics would be registered. The DNDRP is ideally suited for this, as all prescriptions on oral anticoagulants in Denmark receive reimbursement and are therefore recorded. Regarding TEE during primary admission, ideally we should have investigated the discharge summaries of every procedure with LOS ≤5 days. However, as TEE are serious complications they would require prolonged hospitalization. Thus, LOS in all 7 patients with TEE during primary admission was >5 days (fig. 3b).

The local guidelines for thrombosis prophylaxis in the participating departments was 6-10 days after discharge when LOS >5 days, and therefore it may be problematic that we do not have exact data on duration of prophylaxis for the secondary cohort. However, this does not change the conclusion; that prophylaxis only during admission is safe in THA and TKA with LOS ≤5 days. It could also be argued that our study should have been carried out as a RCT. However we did not attempt to compare 2 types of treatment. Instead, for complex medical situations detailed cohort studies have been proposed as a viable, and sometimes preferable, alternative.[41;42] In this context, a post-hoc analysis assuming a 2% baseline risk of symptomatic VTE with extended LMWH prophylaxis of about 35 days[2] found the actual power of our study to be 99% due the large number of patients. Whether our cut-off of 5 days LOS is an optimal way of deciding on duration of prophylaxis is uncertain, but it seems unlikely that patients with a satisfactory fast-track procedure

would have longer LOS.[33;37] However, it is worth noticing that >75% of procedures were followed by LOS, and consequently thromboprophylaxis, for ≤3 days and that about 95% of all procedures had LOS ≤5 days.

In conclusion, we found low rates of TEE and VTE after primary elective fast-track THA and TKA with thromboprophylaxis only during hospitalization in patients with LOS ≤5 days. These results support previous findings from other types of surgery, suggesting that guidelines on postoperative thromboprophylaxis need reconsideration in modern elective surgical procedures.

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Contributions: CCJ updated the initial protocol, registered the trial, undertook all data gathering, performed all statistical analyses, produced all tables and figure, wrote the first manuscript draft, revised it and submitted it for publication. MKJ wrote the initial protocol, helped implement the study setup and helped revise the manuscript. KS supervised the initial protocol, implemented the study setup at Aarhus hospital, conducted the interim analysis and randomized sample audit and helped revising the manuscript. TBH helped develop the initial protocol, implemented the study setup at regional hospital Holstebro, conducted the randomised sample audit and helped revising the manuscript. HK supervised the initial protocol, supervised the work done by CCJ, contributed to data analysis and helped to draft and revise the manuscript. HH, PKA, LTH, and MBL helped develop the initial protocol, implemented the study setup at their respective study locations and revised the manuscript. All authors approved of the final version to be published. CCJ had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

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Conflicts of interests: HH and HK are board members of the Health Care initiatives, Biomet Rapid Recovery. The remaining authors declare no potential conflicts of interest.

Ethics: The Regional Ethics Committee waived the need for study approval. Permission was acquired from the Danish National Board of Health j.nr:3-3013-56/1/HKR and the Danish Data Protection Agency j.nr: 2007-58-0015 to review and store patient records without informed consent.

Trial registration: The study was registered on ClinicalTrials.gov ID: NCT01557725 prior to acquisition and analysis of data.

Data sharing: Patient level data and full dataset available from the corresponding author. Consent was not obtained but the presented data are anonymised and risk of identification is low.

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Legends:

Figure 1.

Flowchart of the study population. THA: total hip arthroplasty TKA: total knee arthroplasty

Figure 2

Cumulated incidence of symptomatic venous thromboembolic events

Figure 3a and 3b

Timing of type of thromboembolic events in the early discharge cohort (3a) and the "unsuccessful" early discharge cohort (3b) TEE: thromboembolic event VTE: venous thromboembolic event. Dotted line marks postoperative day 30.

Table 1.
Preoperative patient characteristics and prophylaxis duration

Characteristic	Early discharge N: 4659	"Unsuccessful" early discharge N: 265	P	Characteristic	Early discharge N: 4659	"Unsuccessful" early discharge N: 265	P
Age (SD)	66.8 (10.7)	73.0 (12.1)	<0.001	BMI (SD)	28.4 (5.1)	27.9 (5.7)	0.110
<50	313 (6.7)	11 (4.2)		<18.5	35 (0.8)	5 (1.9)	
50-60	855 (18.4)	28 (10.6)		18.5-24.9	1186 (25.6)	79 (30.4)	
61-65	779 (16.7)	19 (7.2)		25.0-29.9	1865 (40.2)	102 (39.2)	
66-70	916 (19.7)	34 (12.8)		30.0-39.9	1426 (30.7)	63 (26.0)	
71-75	807 (17.3)	47 (17.7)		≥40	126 (2.7)	11 (3.7)	
76-80	585 (12.6)	50 (18.9)		missing	21 (0.5)	5 (1.9)	
81-86	302 (6.5)	45 (17.0)					
>86	102 (2.2)	31 (11.7)					
Gender			0.002	Joint			0.961
Females	2654 (57.0)	177 (66.8)		THA	2451 (52.6)	139 (52.5)	
Males	2005 (43.0)	88 (33.2)		TKA	2208 (47.4)	126 (47.5)	
Use of compressive stockings			<0.001	Diabetes:			0.426
				T1D	14 (0.3)	2 (0.7)	
yes	250 (5.5)	35 (13.7)		T2D	505 (10.9)	30 (11.5)	
no	4267 (94.5)	220 (86.3)		none	4112 (88.8)	230 (87.8)	
missing	142 (3.0)	10 (3.8)		missing	28 (0.6)	3 (1.1)	
Social situation			<0.001	Hypertension			<0.001
living with others	3117 (66.9)	117 (44.2)		yes	2291 (49.5)	161 (61.2)	
living alone	1502 (32.2)	139 (52.5)		no	2335 (50.5)	102 (38.8)	
nursing home etc.	40 (0.9)	9 (3.4)		missing	33 (0.7)	2 (0.8)	
Use of walking aid			<0.001	Pharmacologically treated PsD			<0.001
yes	1078 (23.7)	142 (55.0)					
no	3469 (76.3)	116 (45.0)		yes	311 (6.7)	33 (12.6)	
missing	112 (2.4)	7 (2.6)		no	4308 (93.3)	228 (87.4)	
				missing	40 (0.9)	4 (1.5)	
Hypercholesterolemia			0.044	Prior cerebral stroke			<0.001
yes	1289 (28.0)	89 (33.7)					
no	3321 (72.0)	175 (66.3)		yes	250 (5.5)	29 (11.2)	
missing	49 (1.1)	1 (0.4)		no	4336 (94.5)	229 (88.8)	
				missing	73 (1.6)	7 (2.6)	
Smoking			0.058	Prior VTE			<0.001
yes	703 (15.2)	51 (19.2)		yes	179 (3.9)	22 (8.5)	
no	3908 (84.8)	209 (80.4)		no	4401 (96.1.0)	261 (91.5)	
missing	48 (1.0)	5 (1.9)		missing	79 (1.7)	6 (2.3)	
Alcohol >2 units daily			0.015	Relative with VTE			0.023
yes	345 (7.5)	9 (3.4)		yes	507 (12.2)	16 (7.1)	
no	4263 (91.5)	252 (96.6)		no	3643 (87.8)	208 (92.9.0)	
missing	51 (1.1)	4(1.5)		missing	509 (10.9)	41 (15.5)	
Pharmacologically treated PD			0.094	Anticoagulative treatment			<0.001
yes	333 (7.2)	26 (10.0)		platelet inhibitors	1284 (26.2)	120 (39.7)	
no	4286 (92.8)	264 (90.0)		none	3375 (68.9)	145 (48.0)	
missing	44 (0.9)	5 (1.9)		missing	0 (0)	0 (0)	

Pharmacologically treated CD			0.005	Duration of prophylaxis:		
yes	418 (9.1)	37 (14.4)		mean (SD)	2.5 (0.91)	N/A
no	4175 (90.9)	220 (85.6)		median (IQR)	2 (2-3)	N/A
missing	66 (1.4)	8 (3.0)				

Data reported as n (%) for counts and mean for continuous variables unless otherwise specified.
N= procedures SD: Standard deviation BMI: body mass index THA: total hip arthroplasty TKA: total knee arthroplasty CD: cardiac disease T1D: type 1 diabetes T2D: type 2 diabetes PD: pulmonary disease PsD: psychiatric disease VTE: venous thromboembolic event LOS: length of hospital stay IQR: Interquartile range N/A: not available

Table 2. Venous thromboembolic events, all thromboembolic events and mortality

Outcomes	All procedures (n:4924)	Early discharge (n:4659)	"Unsuccessful" early discharge (n:265)
PE	10 (0.21; [0.12-0.38])	5 (0.11; [0.05-0.25])	5 (1.99; [0.92-4.27])
Any DVT	16 (0.37; [0.24-0.58])	14 (0.30; [0.18-0.50])	2 (0.67; [0.18-2.38])
Proximal DVT	11 (0.23; [0.13-0.41])	9 (0.19; [0.10-0.36])	2 (0.67; [0.18-2.38])
Any VTE	30 (0.58; [0.41-0.83])	19 (0.41; [0.26-0.64])	7 (2.65; [1.35-5.14])
Any VTE (THA/TKA)	17/13 (0.62; [0.39-0.99]) / (0.53; [0.31-0.90])	15/4 (0.61; [0.37-1.00]) / (0.18; [0.07-0.46])	1/6 (0.65; [0.11-3.60]) / (4.70; [2.31-9.38])
Myocardial infarction	8 (0.17; [0.09-0.32])	7 (0.15; [0.07-0.31])	1 (0.33; [0.06-1.85])
Ischaemic stroke	8 (0.19; [0.10-0.35])	6 (0.13; [0.06-0.28])	2 (0.99; [0.34-2.87])
Transient cerebral ischaemia	7 (0.15; [0.08-0.30])	7 (0.15; [0.07-0.31])	0 (0.33; [0.06-1.85])
Arterial embolus	1 (0.04; [0.01-0.14])	0 (0.00; [0.00-0.08])	1 (0.66; [0.18-2.38])
Any TEE	50 (1.12; [0.87-1.44])	39 (0.84; [0.62-1.15])	11 (4.97; [3.04-8.04])
Any TEE (THA/TKA)	29/21 (1.17; [0.83-1.65]) / (1.05; [0.72-1.53])	27 /12 (1.10; [0.76-1.60]) / (0.54; [0.31-0.94])	2/9 (1.96; [0.67-5.60]) / (8.05; [4.66-13.54])
All-cause mortality	17 (0.42; [0.28-0.64])	13 (0.28; [0.16-0.49])	4 (1.99; [0.92-4.27])
Unrelated to surgery	4 (0.10; [0.04-0.23])	3 (0.06; [0.01-0.20])	1 (0.33; [0.06-1.85])
Surgically related mortality	7 (0.19; [0.10-0.35])	4 (0.09; [0.04-0.23])	3 (1.66; [0.71-3.82])
Death of unknown cause	6 (0.13; [0.06-0.27])	6 (0.13; [0.06-0.28])	0 (0.00; [0.00-1.26])
Fatal PE	1 (0.04; [0.01-0.14])	1 (0.02; [0.00-0.12])	0 (0.33; [0.06-1.85])
Fatal PE/death of unknown cause	7 (0.17; [0.09-0.32])	7 (0.15; [0.07-0.31])	0 (0.33; [0.06-1.85])
Any VTE or death of unknown cause	32 (0.71; [0.52-0.98])	25 (0.54; [0.37-0.80])	7 (2.65; [1.35-5.14])
Any TEE or death of unknown cause	56 (1.25; [0.98-1.59])	45 (0.97; [0.73-1.29])	11 (4.97; [3.04-8.04])

Data reported as counts n (%; [95%CI]) VTE: venous thromboembolic events TEE: thromboembolic events PE: Pulmonary embolism DVT: deep venous thrombosis THA: total hip arthroplasty TKA: total knee arthroplasty

Thrombosis prophylaxis only during hospitalization in fast-track hip and knee arthroplasty, a prospective cohort study

Christoffer C Jørgensen*, Michael K Jacobsen, Kjeld Soeballe, Torben B Hansen, Henrik Husted, Per Kjærsgaard-Andersen, Lars T Hansen, Mogens B Laursen, and Henrik Kehlet

Section for Surgical Pathophysiology 4074, The Juliane Marie Centre, Rigshospitalet, Copenhagen University, 2100 Copenhagen, Denmark Christoffer C Jørgensen Research fellow

Department of Orthopaedics, Aarhus University Hospital, Aarhus University, Brendstrupgårdsvej 100, 8200 Aarhus N, Denmark Michael K Jacobsen Orthopaedic Surgeon

Department of Orthopaedics, Aarhus University Hospital, Aarhus University, Brendstrupgårdsvej 100, 8200 Aarhus N, Denmark Kjeld Soeballe Professor

Department of Orthopaedics, Regional Hospital Holstebro, Aarhus University, Lægårdvej 12 7500 Holstebro, Denmark Torben B Hansen Professor

Orthopaedic Department, Hvidovre University Hospital, Kettegård Alle 30, 2650 Hvidovre, Denmark Henrik Husted Senior Consultant

Department of Orthopedics, Vejle Hospital, University of Southern Denmark, Kabbeltoft 25, 7100 Vejle, Denmark Per Kjærsgaard-Andersen Associate Professor

Orthopaedic Department, Sydvestjysk Hospital Esbjerg/Grindsted, Engparken 1, 7200 Grindsted, Denmark Lars T Hansen Senior Consultant

Aalborg University Hospital Northern Orthopaedic Division, Aalborg University, Højgårdsvej 11, 9640 Farsø, Denmark Mogens B Laursen Associate Professor

Section for Surgical Pathophysiology 4074, The Juliane Marie Centre, Rigshospitalet, Copenhagen University, 2100 Copenhagen, Denmark Henrik Kehlet Professor

All authors are members of The Lundbeck Foundation Centre for Fast-track Hip and Knee Replacement 2100 Copenhagen, Denmark.

*Corresponding author: christoffer.calov.joergensen@regionh.dk Section for Surgical Pathophysiology 4074, The Juliane Marie Centre, Rigshospitalet, Copenhagen University, 2100 Copenhagen, Denmark

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Abstract:

Objectives: International guidelines recommend thrombosis prophylaxis after total hip (THA) and knee arthroplasty (TKA) for up to 35 days. However previous studies often have hospital stays (LOS) of 8-12 days and not considering early mobilisation, which may reduce incidence of venous thromboembolic events (VTE). We investigated the incidence of any symptomatic thromboembolic events (TEE) with only in-hospital prophylaxis if LOS ≤5 days after fast-track THA and TKA.

Design: A prospective descriptive multicenter cohort study in fast-track THA and TKA from February 2010 to December 2011, with complete 90-days follow-up through the Danish National Patient Registry and patient files.

Setting: 6 Danish high-volume centers with a similar standardized fast-track setup, including spinal anaesthesia, opioid-sparing analgesia, early mobilization, functional discharge criteria and discharge to own home.

Participants: 4924 consecutive unselected unilateral primary THA and TKAs in patients ≥18 years with no preoperative use of continuous "potent" anticoagulative therapy (vitamin-K antagonists).

Exposure: Prophylaxis with low molecular weight heparin or factor Xa-inhibitors only during hospitalization when LOS ≤5 days.

Outcomes: Incidence of symptomatic TEE, VTE and VTE-related mortality ≤90 days postoperatively.

Results: LOS ≤5 days and thromboprophylaxis only during hospitalization occurred in 4659 procedures (94.6% of total). Median LOS and prophylaxis duration was 2 days (interquartile range: 2-3) with 0.84% [95%CI: 0.62-1.15] TEE and 0.41% [0.26-0.64] VTE during 90-days follow-up. VTE consisted of 5 pulmonary embolisms (0.11% [0.05-0.25]) and 14 deep venous thrombosis (0.30% [0.18-0.50]). There were 4 (0.09% [0.04-0.23]) surgery-related deaths, of which 1 (0.02% [0.00-0.12]) was due to pulmonary embolism, and 6 (0.13% [0.06-0.28]) deaths of unknown causes after discharge.

Conclusions: The low incidence of TEE and VTE suggests that in-hospital prophylaxis only, is safe in ~~unselected~~ fast-track THA and TKA patients with LOS of ≤5 days. ~~Thrombosis~~

prophylaxisGuidelines on thromboprophylaxis guidelines may need reconsideration in fast-track elective surgery.

Trial Registration: ClinicalTrials.gov: NCT01557725 Word count: 299/300

Article summary:

Article focus:

- Total hip (THA) and knee arthroplasty (TKA) are considered high risk procedures for venous thromboembolic events (VTE).
- Thrombosis prophylaxis for 14-35 days postoperatively is recommended, but previous studies have a length of stay in hospital (LOS) of 8-12 days and do not consider early mobilisation.
- We evaluated the incidence of symptomatic thromboembolic events (TEE) 90 days after fast-track THA and TKA in unselected patients with LOS ≤5 days and thromboprophylaxis only during hospitalisation.

Key messages:

- Incidence of symptomatic TEE and VTE was comparable or lower than in studies with 14-35 days of postoperative thromboprophylaxis.
- Thrombosis prophylaxis only during hospitalisation is safe in fast-track THA and TKA with early mobilisation and LOS ≤5 days

Strengths and Weaknesses:

- A prospective multicentre trial in a large cohort of consecutive unselected patients, with a standardized perioperative fast-track setup.
- Complete 90-days follow-up through the Danish National Patient Registry and patient files.

- Registration of TEE was based on review of patient files, any TEE not mentioned in these would not have been registered.

Introduction

Venous thromboembolic events (VTE) such as deep venous thrombosis (DVT) and pulmonary embolism (PE) are well documented risks in hospitalized patients[1]. Surgery presents an independent risk factor for such events, due to both the surgical trauma and postoperative immobilization. Consequently, guidelines for postoperative thrombo~~sis~~ prophylaxis have been developed in both general and orthopedic surgery.[2-4] However, the type and duration of prophylaxis following elective surgery is debatable.[5-7] ~~In~~ For example, the American College of Chest Physicians (ACCP) recommends either mechanical prophylaxis using intermittent pneumatic compressive devices (IPCD) (Grade 1C), or pharmacological prophylaxis (Grade 1B), for up to 35 days (Grade 2B) after total hip (THA) and knee arthroplasty (TKA),[2] ~~while~~ whereas the American Academy of Orthopedic Surgeons find the evidence inconclusive and decide the duration of thromboprophylaxis on an individual basis.~~duration of prophylaxis to be decided individually.~~[8] Much of the evidence regarding duration of thrombo~~sis~~ prophylaxis after orthopedic surgery ~~is~~ has originat~~ing~~ed from large randomized clinical trials (RCT) in THA and TKA with prophylaxis of 10-35 days,[9-13] and these studies also contribute to guidelines in general surgery.[3] However, the pathophysiological mechanisms of thrombosis have not been addressed in the RCTs, which often have long length of stay (LOS) and lack focus on early mobilization, despite ~~that~~ the fact that early mobilization per se may reduce the need for thrombo~~sis~~ prophylaxis.[14]

Fast-track surgery has been developed to improve recovery by using evidence based care principles with multimodal opioid-sparing analgesia, reduction of the surgical stress-response, optimized fluid treatment, adjustment of the use of drains and catheters, and early mobilization. These efforts have resulted in improved outcome following various procedures such as colonic surgery and

~~gynecological~~gynaecological procedures,[15] and major joint arthroplasty.[16] It has been suggested that reassessment of thromboembolic risk in elective surgery is needed due to few incidences of VTE,[5;17] and preliminary data have supported that fast-track THA and TKA may decrease risk of VTE and thereby the need for prolonged prophylaxis.[6;18] Consequently, we designed a large prospective cohort study in unselected consecutive patients having fast-track THA or TKA, with thrombo~~sis~~ prophylaxis only during hospitalization when LOS was ≤5 days. We hypothesized there would be no increase in symptomatic TEE and VTE with prophylaxis only during hospitalization compared to previous data with prophylaxis of 10-35 days.

Methods:

We investigated consecutive unselected primary elective unilateral THA and TKA between February 1st 2010 and December 1st 2011 in patients ≥18 years with a Danish social security number and no prescriptions on "potent" ~~anticoalgulative~~anticoagulant therapy (i.e. vitamin-K antagonists, dabigatran, rivaroxaban) ≤6 months preoperatively. Procedures in patients with more than 1 THA or TKA during the study period were excluded if <45 days between operations. Five departments participated throughout the study period, with a sixth department pausing between March 2010 and April 2011. All departments had a known mean LOS of about 3-4 days, with a similar fast-track setup including mobilization on day of surgery, identical functional discharge criteria and discharge to own home.[19] Patients with preoperative use of platelet inhibitors (acetylic salicylic acid, clopidogrel, dypiridamol etc.) ceased treatment 3-5 days prior to admission and resumed treatment the day after surgery. All patients completed a preoperative questionnaire on characteristics and co-morbidity which was then entered into the Lundbeck Foundation Centre Database (LCDB)[20] (Appendix 1.). Thrombo~~sis~~ prophylaxis was only given during hospitalization in patients with LOS of ≤5 days. If LOS >5 days, prophylaxis was prescribed by the attending

surgeon according to local guidelines. First dose of prophylaxis was given 6-8 hours after surgery and consisted of either: rivaroxaban (Xarelto, Bayer Pharma, Berlin, Germany) 10 mg/day, enoxaparin (Klexane, Sanofi-Aventis, Paris, France) 4000 I.U./day, dalteparin (Fragmin, Pfizer Health Care, N.Y, U.S) 5000 I.U./day or fondaparinux (Arixtra, GlaxoSmithKline, London, U.K.) 2.5mg/day. No departments used IPCD. An interim analysis and a random-sample audit on treatment and data completion, were conducted and approved by the steering committee in 2011 (Appendix 2).

Preoperative data was cross-referenced with the Danish National Patient Registry (DNPR) regarding LOS and 90-days readmissions (including emergency room contacts, but excluding outpatient visits as clinical practice on treatment of TEE in Denmark includes an initial admission to hospital[21]). LOS was defined as number of postoperative nights in hospital (including transferal to other departments) till discharge to the patients' own home. DNPR registers all hospitalizations (including transferals, diagnoses and surgical procedures) at Danish hospitals, allowing information on LOS and readmissions regardless of localization. ~~As~~ R~~r~~eporting is mandatory for receiving reimbursement ensuring completeness of data of about 99.4%.[22;23]~~, complete follow-up is ensured.~~

To detect TEE during primary admission the complete medical records of patients with diagnosis codes related to TEE according to the International Classification of Diseases 10th revision, all transfers to other wards, and the discharge summary of any patients with LOS ≥5 days were investigated. In case of readmission ≤90-days, discharge files and/or patient files were investigated with regards to relation to surgery.[20] Criteria for TEE were predefined as: DVT confirmed by ultrasound, PE confirmed by spiral-CT, ventilation-perfusion scintigraphy or pathological removal of embolus and MI with rise in biomarkers and ischemic symptoms, diagnostic electrocardiogram changes, primary coronary intervention or coronary bypass graft. Ischemic stroke was defined as neurological symptoms >24 hours and a positive CT-scan, and transient ischemic attack (TIA) as

neurological symptoms lasting less than 24 hours and no new changes on CT-scan. Mortality was obtained through the Central Office of Civil Registration using unique Danish social security numbers. Cause of death was obtained from the patient files/autopsies. In case of death outside hospital with no autopsy, the patient's general practitioner was contacted regarding cause of death. Adjudication of discharge summaries and patient files, apart from reasons for LOS ≥5 days and death during admission, was blinded with regards to duration of thrombosis prophylaxis. Adjudication was done by the first author (CJ), and in case of possible TEE the first author (CJ) and senior author (HK) adjudicated cases together.

All prescriptions on "potent" anticoagulant~~ive~~ therapy and platelet inhibitors 6 months before and 3 months after surgery were investigated using The Danish National Database of Reimbursed Prescriptions (DNDRP). During the study period all prescriptions on "potent" anticoagulant~~ive~~ treatment received government reimbursements securing 100% completeness of data.[24] Patients without prescriptions on anticoagulative therapy, but answering "yes" in the questionnaire were assumed to use platelet inhibitors. In 21 procedures in patients with LOS ≤5 days we found only postoperative prescriptions on "potent" anticoagulative therapy. All hospital contacts of these patients were reviewed and, if insufficient for determining the cause of the prescription, we contacted their general practitioner. In 2 cases the prescription was due to DVT found during outpatient visits without regular hospital admission, while 7 cases were due to perioperative atrial-flutter with treatment initiated ≥22 days after discharge. These were all retained in the study cohort. The remaining 12 cases were due to specific surgical considerations, discharge from other wards or readmission with treatment despite unverified VTE. These were considered protocol violations and included in the ~~secondary~~ unsuccessful early discharge cohort.

Outcomes

Primary outcome was occurrence of symptomatic TEE (DVT, PE, arterial embolism (AE), MI, ischaemic stroke or TCA) and VTE (DVT or PE) 90 days after THA/TKA in patients with prophylaxis only during admission.

Secondary outcome was occurrence of the primary outcome in patients with thrombo~~sis~~ prophylaxis after discharge. Bleeding-events ~~was~~ were protocolled as a safety endpoint, but was hindered by incomplete registration. A separate analysis on patients not in the LCDB was done to identify potential bias.

Statistics and power calculation

A pre-study power analysis using a two-tailed one sample difference from constant test, found that 2838 patients were needed to detect a 1% increase in TEE when assuming a TEE rate of 3%, β: 82 and α: 0.05. Correspondingly, 2076 patients were needed to detect a 1% increase in symptomatic VTE assuming a 90-days baseline risk of 2%.[2]

Data were tested for normality using q-q plots and histograms. Comparisons of continuous data were made using Mann-Whitney U-test and t-test and for categorical data with χ^2-test or Fishers exact-test, as appropriate. Events (incident cases) are reported as actual number and percentage with 95% confidence intervals (95%CI) using http://www.vassarstats.net/prop1.html. All other analysis was done in SPSS v. 20 (IBM Corporation, Armonk, NY)

Results

~~*Primary outcome*~~

Total cohort

A total of 4924 procedures in 4718 patients were included. Median LOS was 2 days (IQR: 2-3), and readmissions occurred after 400 (8.1%) of all procedures. We found 50 (1.12%) TEE, of which 30

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(0.58%) were VTE. Symptomatic in-hospital TEE occurred after 7 (0.14% [0.07-0.29]) procedures of which 4 (0.08% [0.03-0.21]) were VTE. All-cause mortality was 0.42%, including one fatal PE (0.04%) and 6 deaths of unknown causes (0.1%) (table 2).

~~Of a total of 4924 included procedures,~~ *Successful early discharge cohort*

~~4659 (94.6%) procedures in 4455 patients had~~ Early discharge with LOS ≤5 days occurred in 4659 (94.6%) procedures in 4455 patients ~~and comprised the study population~~ (figure 1). These patients had a ~~M~~mean age ~~was~~of 66.8 years (SD~~:10.7~~: 10.7) with a median LOS and prophylaxis duration of 2 days (interquartile range (IQR): 2-3) (table 1). ~~and~~There were 353 (7.6%) surgery-related readmissions of which 2.9% were due to "surgical" morbidity (hip displacements, prosthesis infections, knee manipulation etc.) and 4.7% were due to "medical" morbidity, such as anaemia, cardiac arrhythmia, pneumonia, unverified prosthesis infection and pain. ~~(table 1).~~

A total of 39 (0.84%) TEE were found within 90 days, of which 24 (0.52% 95%CI: 0.35-0.77) occurred during the first postoperative month. One patient was readmitted twice due to ischemic strokes on postoperative days 8 and 46. According to the medical records, the second stroke was cardiac in origin as the patient was known with atrial flutter, but treated only with acetylsalicylic acid due to gastrointestinal bleeding. There were 19 (0.41%) symptomatic VTE (figure 2 and 3a), consisting of 5 (0.11%) PEs and 14 (0.30%) DVTs of which 9 were proximal (table 2). Median time to VTE was 21 days (IQR: 8-39), with 12 VTE ≤30 days postoperatively (30-day VTE-rate: 0.26% 95%CI: 0.15-0.45).

There were 13 (0.28%) deaths during follow-up. Of these 3 (0.06%) were unrelated to surgery (cancer and gastric morbidity >45 days after surgery) and 6 (0.13%) were of unknown causes outside hospital (postoperative day: 19,27,36,44,48, and 85). Thus, 4 (0.09%) deaths were confirmed surgically related (table 2), 1 due to an autopsy confirmed PE on postoperative day 41

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and 1 due to intracerebral bleeding on day 26. The remaining 2 deaths were due to paralytic ileus on postoperative day 36 and sepsis on postoperative day 24.

~~*Secondary outcome*~~*The "unsuccessful" early discharge cohort*

This ~~-~~cohort of 265 (5.4%) procedures in 263 patients (figure 1), was older and ~~with~~ had more co-morbidity than the ~~study~~ early discharge cohort (table 1). Median LOS was 7 days (IQR: 6-9) with 47 (17.7%) surgically-related readmissions (5.7% "surgical" and 12.0% "medical" morbidity). Of 11 (4.97%) TEE with 7 (2.65%) VTE (table 2), 7 and 4, respectively, occurred during index hospitalization consequently resulting in LOS >5 days. ~~Thus, the total occurrence of symptomatic in-hospital TEE and VTE during primary admission in the complete material of 4924 procedures from the LCDB was 0.14% (0.07-0.29) and 0.08% (0.03-0.21) respectively.~~

Of the 4 (1.51% [95%CI: 0.59-3.82]) TEE after discharge, ~~in the secondary cohort~~ 1 (0.38% [0.07-2.11]) was an ischaemic stroke and 3 were VTE (1.13% [0.38-3.27]), with 2 PEs (0.75% [0.21-2.70]) and 1 DVT (0.38% [0.07-2.11]). Median time to VTE was 3 days (IQR: 2-53) (figure 3b) ~~in the secondary cohort~~. We found 3 (1.13%) surgically-related deaths, 1 death unrelated to surgery (paralytic ileus on day 70 in a patient refusing treatment) and no VTE-related deaths or deaths of unknown causes (0.00% [0.00-1.43]).

Patients not in LCDB (3.6%)

In these 194 (108 THA/86 TKA) procedures in 191 patients, mean age was 68.5 years (SD: 11.0) and 178 (91.8%) had LOS ≤5 days. In these 178 procedures there was 1 (0.56% [0.10-3.11]) readmission due to an MI, no VTE and no deaths. No further analysis was done as no bias was apparent compared to the study population.

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Discussion

In this prospective study in fast-track primary THAs and TKAs ~~with LOS ≤5 days and in-hospital thrombosis prophylaxis only~~, we found 90-days postoperative rates of symptomatic TEE and VTE of 0.84% and 0.41% respectively, in patients with LOS ≤5 days and in-hospital thromboprophylaxis only ~~respectively~~. The patients receiving prophylaxis only during index hospitalization (median 2 days) contributed 94.6% of the total number of performed procedures, as 5.4% had LOS >5 days and consequently received longer prophylaxis. The study has several strengths, such as a consecutive unselected population including high-risk patients with various types of co-morbidity, a standardized perioperative fast-track setup, and complete detailed 90-days follow-up.

We used any TEE as primary endpoint in order not to overlook a potential worsened outcome. Stroke and MI have been included as safety endpoints in most RCTs[10-12], but are often neglected in reviews and database studies.[25-27] We found no increase in the occurrence of ischemic stroke ~~when comparing~~compared to ~~with~~ previous studies of in-hospital ~~occurrences~~ stroke in THA[28] and strokes ≤30 days ~~or with 30 day incidences~~ in both TKA and THA,[29] ~~,~~ despite our follow-up being 90 days and not only relying on diagnostic codes. Neither was there any apparent increase in the occurrence of MI compared to a recent study which found MI in 0.51% of THA and 0.21% of TKA after 6 weeks.[30] The numbers of symptomatic VTE ~~was~~ were lower or comparable to the RCTs with prophylaxis of 10 to 35 days.[10-13] However, LOS in these RCTs was 8-12 days with unspecified discharge locations, whereas LOS after 94.6% of procedures in our study was ≤5 days until discharge to own home. The long LOS in these studies may include partial immobilization, thereby increasing the risk of VTE and consequently the need for thrombo~~sis~~ prophylaxis. Correspondingly, a previous small-scale study in 247 TKA found a decreased risk of DVT following mobilization within 24 hours of surgery,[14] and an earlier fast-track single-centre study with prophylaxis only

during admission in 1977 THA and TKAs with a mean LOS of about 3.5 days found 0.86% symptomatic VTE within 90 days.[18]

Another main difference between our study and the RCTs is that there was no preoperative selection of patients, ~~our patients were unselected, with~~as duration of prophylaxis depend~~ing~~ed only on discharge within 5 days, regardless of co-morbidity. Thus, our results reflect "everyday patients", whereas the exclusion criteria in the RCTs may have reduced occurrences of TEE.[8;31] The only excluded patients in our study were those using preoperative "potent" anticoagulant~~ive~~ therapy, since they obviously needed continuation after discharge. Two Danish nationwide studies found symptomatic VTE in >1% of THA and TKA despite prolonged prophylaxis, and that the incidence was increasing across the study periods (1995-2007).[26;32] The difference between these data and ours may be due to the fast-track set-up including early mobilization in our study, and since LOS in Denmark was about 11 days in year 2000.[33]

The occurrence of in-hospital TEE in the total 4924 procedures in the LCDB was low (0.14%), and particularly the incidence of symptomatic in-hospital VTE (<0.10%) was lower than the 0.5% in THA and 1.0% in TKA found in a recent review.[25] Although the timing of VTE, ~~-~~with the majority occurring within the first month is consistent with previous studies,[2;34] we believe that the low incidence questions the benefits of prolonged prophylaxis in all patients after fast-track THA and TKA. Further studies are needed to identify whether certain patient subgroups may benefit from more extensive or intensive prophylaxis, and how to avoid in-hospital TEE while patients are receiving recommended treatment. However, due to the few events the numbers of patients needed for such studies pose major challenges.

Finally, we report both confirmed VTE-related death and a "worst case" scenario, with death of unknown causes being considered VTE-related, despite that cause of death after THA/TKA often is

found unrelated to VTE.[35] Thus, we found only one verified fatal PE, and a 90-days all-cause mortality comparable to or lower than previous studies.[27;36-38]

The ~~secondary~~ "unsuccessful" early discharge cohort ~~with LOS >5 days~~ was older with more co-morbidity and readmissions. This is not surprising, as we have previously found an association with LOS and readmissions after fast-track THA and TKA in such patients.[20] There were about 2% PEs in these patients, but this is in accordance with co-morbidities such as cardiac disease or previous TEE, being associated with cardiac and thromboembolic complications after arthroplasty.[27] Furthermore, complications per se may lead to prolonged LOS and thereby longer prophylaxis. Thus, about 60% of TEE and VTE in this cohort occurred during primary admission. However, it does not argue against our conclusion that prophylaxis only during admission is safe when LOS ≤5 days.

Our study has limitations, foremost regarding the follow-up which was based on hospital contacts. However, although the reliability of diagnostic codes for VTE in DNPR may be low,[39] completion of data regarding somatic admissions ~~DNPR~~ is close to 100% ~~records all readmissions independent of site of index operation.~~[22;39]~~, and~~Consequently, we investigated ~~these~~ all admissions through discharge summaries and patient files instead of relying only on diagnostic codes, as often done in large-scale cohort studies.[26;32;40] Although TEE may have been left out of the discharge summary, this seems unlikely, as they require treatment after discharge. We also used the DNDRP to detect procedures followed by a postoperative prescription of potent ~~antocoagulat~~anticoagulant~~ive~~ therapy, thereby ensuring that~~finding~~ any TEE diagnosed in outpatient clinics would be registered. The DNDRP is ideally suited for this, as all prescriptions on oral anticoagulants~~ives~~ in Denmark receive reimbursement and are therefore recorded. Regarding TEE during primary admission, ideally we should have investigated the discharge summaries of every procedure with LOS ≤5 days. However,

as TEE are serious complications they would require prolonged hospitalization. Thus, LOS in all 7 patients with TEE during primary admission was >5 days (fig. 3b).

The local guidelines for thrombosis prophylaxis in the participating departments was 6-10 days after discharge when LOS >5 days, and therefore it may be problematic that we do not have exact data on duration of prophylaxis for the secondary cohort. However, this does not change the conclusion; that prophylaxis only during admission is safe in THA and TKA with LOS ≤5 days. It could also be argued that our study should have been carried out as a RCT. However we did not attempt to compare 2 types of treatment. Instead, for complex medical situations detailed cohort studies have been proposed as a viable, and sometimes preferable, alternative.[41;42] In this context, a post-hoc analysis assuming a 2% baseline risk of symptomatic VTE with extended LMWH prophylaxis of about 35 days[2] found the actual power of our study to be 99% due the large number of patients. Whether our cut-off of 5 days LOS is an optimal way of deciding on duration of prophylaxis is uncertain, but it seems unlikely that patients with a satisfactory fast-track procedure would have longer LOS.[33;37] However, it is worth noticing that >75% of procedures were followed by LOS, and consequently thrombo~~sis~~ prophylaxis, for ≤3 days and that about 95% of all procedures had LOS ≤5 days.

In conclusion, we found low rates of TEE and VTE after primary elective fast-track THA and TKA with thrombo~~sis~~ prophylaxis only during hospitalization in ~~unselected~~ patients with LOS ≤5 days. These results support previous findings from other types of surgery, suggesting that guidelines on postoperative thrombo~~sis~~ prophylaxis need reconsideration in modern elective surgical procedures.

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Contributions: CCJ updated the initial protocol, registered the trial, undertook all data gathering, performed all statistical analyses, produced all tables and figure, wrote the first manuscript draft, revised it and submitted it for publication. MKJ wrote the initial protocol, helped implement the study setup and helped revise the manuscript. KS supervised the initial protocol, implemented the study setup at Aarhus hospital, conducted the interim analysis and randomized sample audit and helped revising the manuscript. TBH helped develop the initial protocol, implemented the study setup at regional hospital Holstebro, conducted the randomised sample audit and helped revising the manuscript. HK supervised the initial protocol, supervised the work done by CCJ, contributed to data analysis and helped to draft and revise the manuscript. HH, PKA, LTH, and MBL helped develop the initial protocol, implemented the study setup at their respective study locations and revised the manuscript. All authors approved of the final version to be published. CCJ had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

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Conflicts of interests: HH and HK are board members of the Health Care initiatives, Biomet Rapid Recovery. The remaining authors declare no potential conflicts of interest.

Ethics: The Regional Ethics Committee waived the need for study approval. Permission was acquired from the Danish National Board of Health j.nr:3-3013-56/1/HKR and the Danish Data Protection Agency j.nr: 2007-58-0015 to review and store patient records without informed consent.

Trial registration: The study was registered on ClinicalTrials.gov ID: NCT01557725 prior to acquisition and analysis of data.

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Legends:

Figure 1.

Flowchart of the study population. THA: total hip arthroplasty TKA: total knee arthroplasty

Figure 2

Cumulated incidence of symptomatic venous thromboembolic events

Figure 3a and 3b

Timing of type of thromboembolic events in the ~~study~~ early discharge cohort (3a) and the ~~secondary~~ "unsuccessful" early discharge cohort (3b) TEE: thromboembolic event VTE: venous thromboembolic event. Dotted line marks postoperative day 30.

Table 1.
Preoperative patient characteristics and prophylaxis duration

Characteristic	~~Study cohort~~Early discharge N: 4659	~~Secondary cohort~~ "Unsuccessful" early discharge N: 265	P	Characteristic	~~Early Study cohort N~~discharge N: 4659	"Unsuccessful" early discharge ~~Secondary cohort~~ N: 265	P
Age (SD)	66.8 (10.7)	73.0 (12.1)	<0.001	BMI (SD)	28.4 (5.1)	27.9 (5.7)	0.110
<50	313 (6.7)	11 (4.2)		<18.5	35 (0.8)	5 (1.9)	
50-60	855 (18.4)	28 (10.6)		18.5-24.9	1186 (25.6)	79 (30.4)	
61-65	779 (16.7)	19 (7.2)		25.0-29.9	1865 (40.2)	102 (39.2)	
66-70	916 (19.7)	34 (12.8)		30.0-39.9	1426 (30.7)	63 (26.0)	
71-75	807 (17.3)	47 (17.7)		≥40	126 (2.7)	11 (3.7)	
76-80	585 (12.6)	50 (18.9)		missing	21 (0.5)	5 (1.9)	
81-86	302 (6.5)	45 (17.0)					
>86	102 (2.2)	31 (11.7)					
Gender			0.002	Joint			0.961
Females	2654 (57.0)	177 (66.8)		THA	2451 (52.6)	139 (52.5)	
Males	2005 (43.0)	88 (33.2)		TKA	2208 (47.4)	126 (47.5)	
Use of compressive stockings			<0.001	Diabetes:			0.426
				T1D	14 (0.3)	2 (0.7)	
yes	250 (5.5)	35 (13.7)		T2D	505 (10.9)	30 (11.5)	
no	4267 (94.5)	220 (86.3)		none	4112 (88.8)	230 (87.8)	
missing	142 (3.0)	10 (3.8)		missing	28 (0.6)	3 (1.1)	
Social situation			<0.001	Hypertension			<0.001
living with others	3117 (66.9)	117 (44.2)		yes	2291 (49.5)	161 (61.2)	
living alone	1502 (32.2)	139 (52.5)		no	2335 (50.5)	102 (38.8)	
nursing home etc.	40 (0.9)	9 (3.4)		missing	33 (0.7)	2 (0.8)	
Use of walking aid			<0.001	Pharmacologically treated PsD			<0.001
yes	1078 (23.7)	142 (55.0)					
no	3469 (76.3)	116 (45.0)		yes	311 (6.7)	33 (12.6)	
missing	112 (2.4)	7 (2.6)		no	4308 (93.3)	228 (87.4)	
				missing	40 (0.9)	4 (1.5)	
Hypercholesterolemia			0.044	Prior cerebral stroke			<0.001
yes	1289 (28.0)	89 (33.7)					
no	3321 (72.0)	175 (66.3)		yes	250 (5.5)	29 (11.2)	
missing	49 (1.1)	1 (0.4)		no	4336 (94.5)	229 (88.8)	
				missing	73 (1.6)	7 (2.6)	
Smoking			0.058	Prior VTE			<0.001
yes	703 (15.2)	51 (19.2)		yes	179 (3.9)	22 (8.5)	
no	3908 (84.8)	209 (80.4)		no	4401 (96.1.0)	261 (91.5)	
missing	48 (1.0)	5 (1.9)		missing	79 (1.7)	6 (2.3)	
Alcohol >2 units daily			0.015	Relative with VTE			0.023
yes	345 (7.5)	9 (3.4)		yes	507 (12.2)	16 (7.1)	
no	4263 (91.5)	252 (96.6)		no	3643 (87.8)	208 (92.9.0)	
missing	51 (1.1)	4(1.5)		missing	509 (10.9)	41 (15.5)	
Pharmacologically treated PD			0.094	Anticoagulative treatment			<0.001
yes	333 (7.2)	26 (10.0)		platelet inhibitors	1284 (26.2)	120 (39.7)	
no	4286 (92.8)	264 (90.0)		none	3375 (68.9)	145 (48.0)	
missing	44 (0.9)	5 (1.9)		missing	0 (0)	0 (0)	

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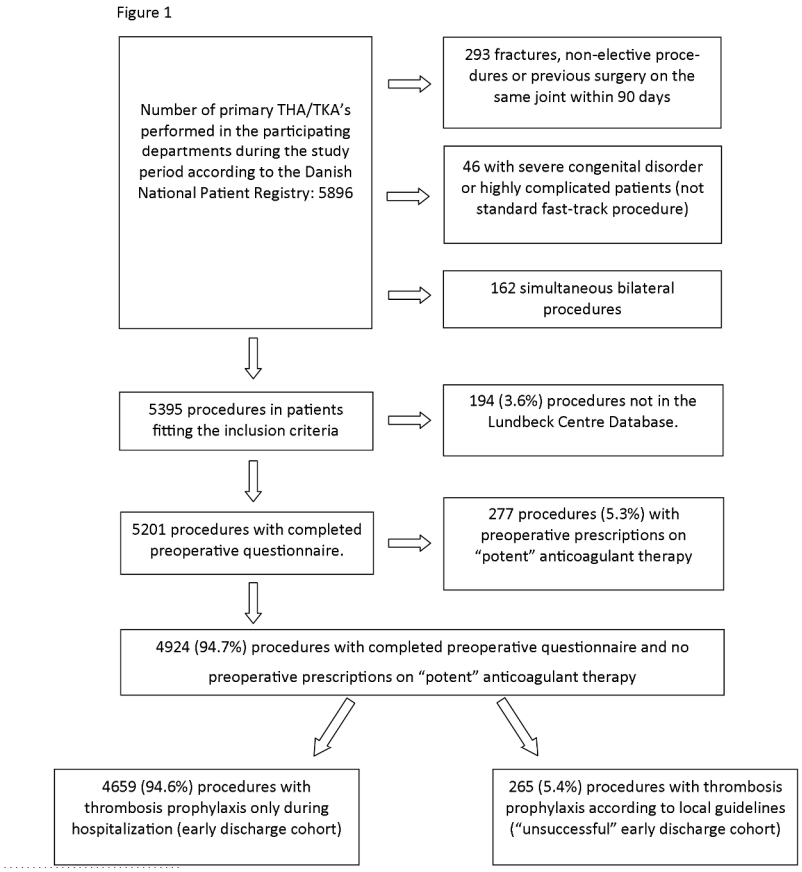
Pharmacologically treated CD			0.005	Duration of prophylaxis:		
yes	418 (9.1)	37 (14.4)		mean (SD)	2.5 (0.91)	N/A
no	4175 (90.9)	220 (85.6)		median (IQR)	2 (2-3)	N/A
missing	66 (1.4)	8 (3.0)				

Data reported as n (%) for counts and mean for continuous variables unless otherwise specified.
N= procedures SD: Standard deviation BMI: body mass index THA: total hip arthroplasty TKA: total knee arthroplasty CD: cardiac disease T1D: type 1 diabetes T2D: type 2 diabetes PD: pulmonary disease PsD: psychiatric disease VTE: venous thromboembolic event LOS: length of hospital stay IQR: Interquartile range N/A: not available

Table 2. Venous thromboembolic events, all thromboembolic events and mortality

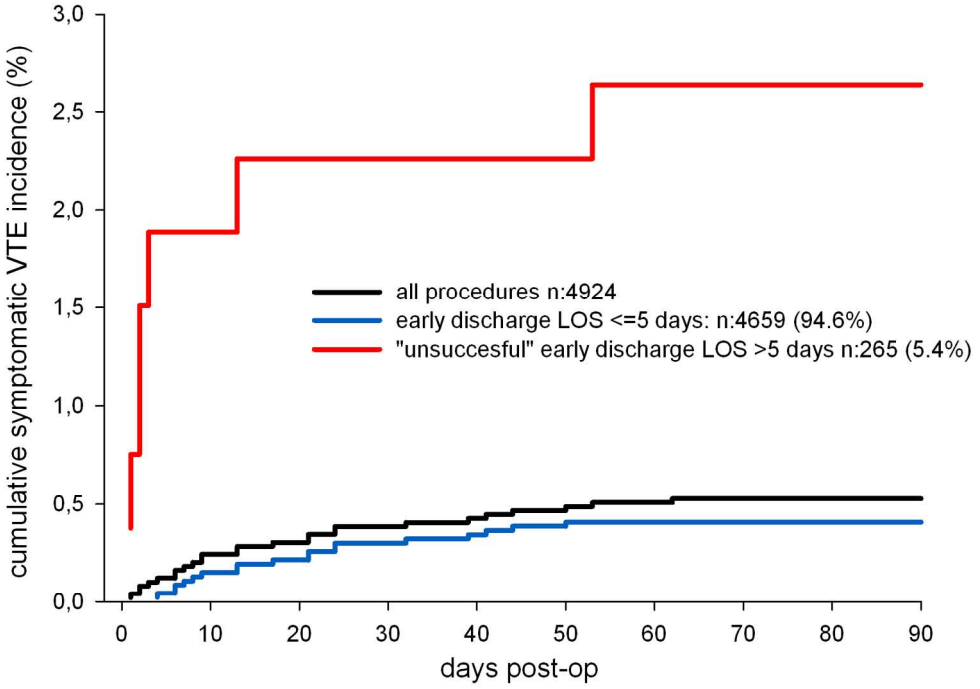
Outcomes	All procedures (n:4924)	Early discharge (n:4659)	"Unsuccessful" early discharge (n:265)
PE	10 (0.21; [0.12-0.38])	5 (0.11; [0.05-0.25])	5 (1.99; [0.92-4.27])
Any DVT	16 (0.37; [0.24-0.58])	14 (0.30; [0.18-0.50])	2 (0.67; [0.18-2.38])
Proximal DVT	11 (0.23; [0.13-0.41])	9 (0.19; [0.10-0.36])	2 (0.67; [0.18-2.38])
Any VTE	30 (0.58; [0.41-0.83])	19 (0.41; [0.26-0.64])	7 (2.65; [1.35-5.14])
Any VTE (THA/TKA)	17/13 (0.62; [0.39-0.99]) / (0.53; [0.31-0.90])	15/4 (0.61; [0.37-1.00]) / (0.18; [0.07-0.46])	1/6 (0.65; [0.11-3.60]) / (4.70; [2.31-9.38])
Myocardial infarction	8 (0.17; [0.09-0.32])	7 (0.15; [0.07-0.31])	1 (0.33; [0.06-1.85])
Ischaemic stroke	8 (0.19; [0.10-0.35])	6 (0.13; [0.06-0.28])	2 (0.99; [0.34-2.87])
Transient cerebral ischaemia	7 (0.15; [0.08-0.30])	7 (0.15; [0.07-0.31])	0 (0.33; [0.06-1.85])
Arterial embolus	1 (0.04; [0.01-0.14])	0 (0.00; [0.00-0.08])	1 (0.66; [0.18-2.38])
Any TEE	50 (1.12; [0.87-1.44])	39 (0.84; [0.62-1.15])	11 (4.97; [3.04-8.04])
Any TEE (THA/TKA)	29/21 (1.17; [0.83-1.65]) / (1.05; [0.72-1.53])	27 /12 (1.10; [0.76-1.60]) / (0.54; [0.31-0.94])	2/9 (1.96; [0.67-5.60]) / (8.05; [4.66-13.54])
All-cause mortality	17 (0.42; [0.28-0.64])	13 (0.28; [0.16-0.49])	4 (1.99; [0.92-4.27])
Unrelated to surgery	4 (0.10; [0.04-0.23])	3 (0.06; [0.01-0.20])	1 (0.33; [0.06-1.85])
Surgically related mortality	7 (0.19; [0.10-0.35])	4 (0.09; [0.04-0.23])	3 (1.66; [0.71-3.82])
Death of unknown cause	6 (0.13; [0.06-0.27])	6 (0.13; [0.06-0.28])	0 (0.00; [0.00-1.26])
Fatal PE	1 (0.04; [0.01-0.14])	1 (0.02; [0.00-0.12])	0 (0.33; [0.06-1.85])
Fatal PE/death of unknown cause	7 (0.17; [0.09-0.32])	7 (0.15; [0.07-0.31])	0 (0.33; [0.06-1.85])
Any VTE or death of unknown cause	32 (0.71; [0.52-0.98])	25 (0.54; [0.37-0.80])	7 (2.65; [1.35-5.14])
Any TEE or death of unknown cause	56 (1.25; [0.98-1.59])	45 (0.97; [0.73-1.29])	11 (4.97; [3.04-8.04])

Data reported as counts n (%; [95%CI]) VTE: venous thromboembolic events TEE: thromboembolic events PE: Pulmonary embolism DVT: deep venous thrombosis THA: total hip arthroplasty TKA: total knee arthroplasty



Flowchart of the study population. THA: total hip arthroplasty TKA: total knee arthroplasty
209x297mm (300 x 300 DPI)

Figure 2



Cumulated incidence of symptomatic venous thromboembolic events
153x120mm (300 x 300 DPI)

Figure 3a

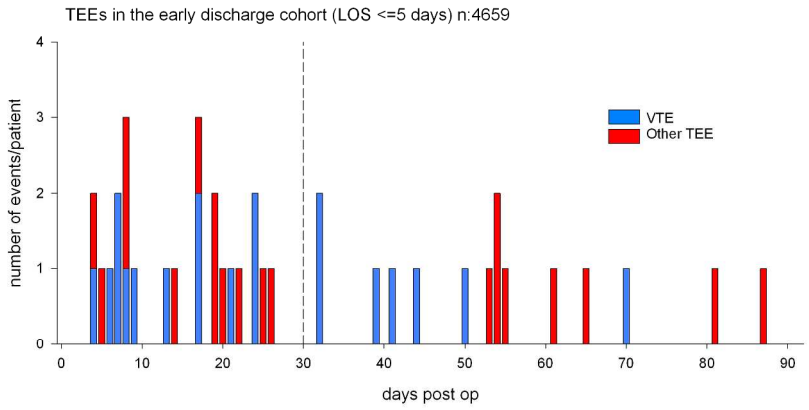
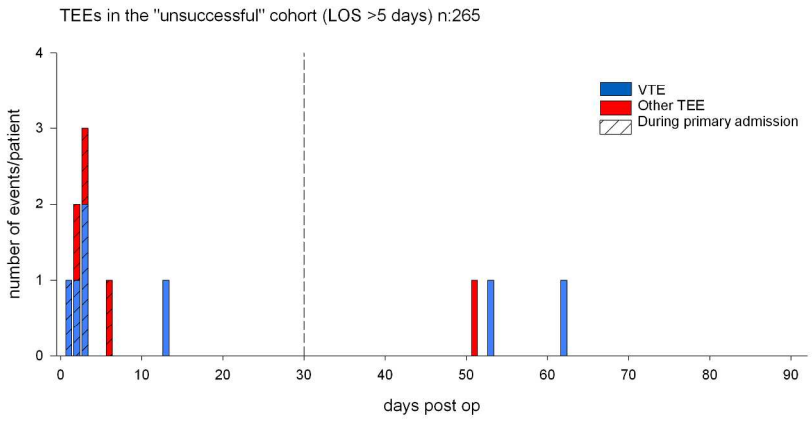


Figure 3b



Timing of type of thromboembolic events in the early discharge cohort (3a) and the "unsuccessful" early discharge cohort (3b) TEE: thromboembolic event VTE: venous thromboembolic event. Dotted line marks postoperative day 30.
209x297mm (300 x 300 DPI)

Appendix 1

Preoperative questionnaire for the Lundbeck Centre Database

Date of surgery
Social security number

Joint (knee/hip)

Height: _____ cm
Weight: _____kg
Haemoglobin level _____ mmol/l
(Taken no more than 1 week previously)
Patients blood type?

Living conditions (alone, with spouse/others, in institution (nursing home etc.))
Smoking (yes/no)
Alcohol >2 units a day (yes/no)
Do you use walking aids prior to admission?
Are you feeling well rested in the morning?
Do you snore loudly?
Do you use compressive stockings regularly?

Do you receive treatment for high cholesterol (yes/no)
Do you receive treatment for high blood pressure (yes/no)
Do you have Type 1 diabetes (yes/no)
Do you have Type 2 diabetes (yes/no)
Have you had a previous cerebral attack?
Have you had a previous venous thromboembolic event?
Do you receive medication for any type of heart disease?
Do you receive medication for any type of pulmonary disease?
Do you receive medication for any type of psychiatric disease?
Do you have a family member who has had a deep venous thrombosis or pulmonary embolus?
Do you have a contraindication for antithrombotic medication?
Do you use antithrombotic medication regularly (courmarin, acetyl salicylic acid etc)?

Results and methods of Interim analysis and random-sample audit

Aim: To elucidate the frequency of asymptomatic deep venous thrombosis (DVT), fatal / non fatal pulmonary embolism (PE), fatal / non fatal acute myocardial infarction (AMI), stroke and transient cerebral ischemic attack (TCI) in patients undergoing elective uni- and bilateral THA /TKA, revision and uni-KA in a fast-track Set-up with short duration (3+/- 2 days) thromboprophylaxis.

Methods: Prospective multicenter study with 5000 patients. Follow-up 90 days.

Data Validation: Once collected, data are transcribed onto paper case-report forms and then entered in the database. In January 2011 a random-sample audit was performed on 250 included patients (50 patients from each center). At that time 2.622 operations were registered in the database. The purpose of the audit was a/: to ensure that included patients received short duration (3 +/-2 days) thromboprophylaxis, b/: to ensure that patients in permanent anticoagulation therapy due to previous venous thrombosis was registered, and c/: to ensure that length of stay met the fast-track criteria.

Results: All 250 patients had a completed questionnaire and no patients with LOS ≤5 days were discharged with prophylaxis except for the few (4.4%) with preoperative PACT. All departments fulfilled the fast-track criteria of mean length of hospital stay ≤3 days.

Data were compared with source documents, and checked for completeness. The result of the audit was satisfactory and approved by the steering committee.

Interim analysis: As of April 15, 2011 3.475 operations were registered in the database (1.598 knee- and 1.877 hip operations). An interim analysis was performed based on patients with complete 90 days follow-up (2.405 patients, 1.089 hips and 1.316 knees).

Table I.
Incidence of thromboembolic events (TEE) and deaths ≤90 days after 2.405 elective uni- and bilateral THA / TKA, revision and uni-KA.

	Hip surgery	Knee surgery	Total
Outcome, events pr. 1.00 [CI 99%]			
Stroke	0.09 [0.0 ; 0.6]	0.5 [1.8 ; 12.4]	0.3 [0.1 ; 0.7]
Transient cerebral ischemic attack	0.00 [0.0 ; 0.4]	0.2 [0.4 ; 7.7]	1.2 [0.02 ; 0.4]
Deep venous thrombosis	0.7 [0.3 ; 0.16]	0.5 [1.8 ; 12.4]	0.6 [0.3 ; 1.14]
Pulmonary embolism	0.2 [0.02 ; 0.8]	0.6 [2.2 ; 13.5]	0.4 [0.2 ; 0.9]
Acute myocardial infarction	0.5 [0.1 ; 1.2]	0.5 [1.4 ; 11.3]	0.5 [0.2 ;0.9]
All, events	1.4 [0.7 ; 2.5]	2.0 [1.2 ; 3.1]	1.7 [1.1 ; 2.5]
Deaths	0.4 [0.1 ; 1.1]	0.4 [0.1 ; 1.0]	0.4 [0.1 ; 0.8]
All vascular events (and all deaths)	1.7 [0.9 ; 3.0]	2.3 [1.4 ; 3.5]	20.4 [1.4 ; 2.9]

Primary endpoint: There frequency of vascular events was not increased in patients undergoing elective uni- and bilateral THA / TKA in a fast-track set-up with short duration (3+/- 2 days) thromboprophylaxis (2.04%) compared with current treatment (3%)(1-6).

Safety: No major bleedings has been reported. The frequency of non-major bleedings was not increased (0.08 %) compared with current treatment (1.5 – 1.7 %)(7).

Length of stay**:** The mean length of stay varied from 2.4 nights to 3.6 nights in the participating centers.

References

(1) Pedersen A. Risk Factors for Venous Thromboembolism in Patients Undergoing Total Hip Replacement and Receiving Routine Thromboprophylaxis. JBJS 2010; 92:2156-2164.

(2) Husted H, Otte K, Kristensen B, Ørsnes T, Wong C, Kehlet H. Low risk of thromboembolic complications after fast-track hip and knee arthroplasty. Acta Orthop 2010; 81(5):599-605.

(3) Mantilla CB, Horlocker TT, Schroeder DR, Berry DJ, Brown DL. Frequency of myocardial infarction, pulmonary embolism, deep venous thrombosis, and death following primary hip or knee arthroplasty. Anesthesiology 2002; 96(5):1140-1146.

(4) Ryge C. Epidemiology study in mayor orthopaedic surgery (ESMOS-study), København, faculty of health science, University of Copenhagen. 2008.

(5) Mahomed NN, Barrett JA, Katz JN, Phillips CB, Losina E, Lew RA et al. Rates and outcomes of primary and revision total hip replacement in the United States medicare population. J Bone Joint Surg Am 2003; 85-A(1):27-32.

(6) Williams O, Fitzpatrick R, Hajat S, Reeves BC, Stimpson A, Morris RW et al. Mortality, morbidity, and 1-year outcomes of primary elective total hip arthroplasty. J Arthroplasty 2002; 17(2):165-171.

(7) Eriksson BI, Borris LC, Friedman RJ, Haas S, Huisman MV, Kakkar AK et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. N Engl J Med 2008; 358(26):2765-2775.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1 and 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	Not applicable
		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable
		(*e*) Describe any sensitivity analyses	Not applicable
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	p.8 Fig.1, table 1-2
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	Not applicable
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-9 Figure 3a
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2 p 8-9
		(*b*) Report category boundaries when continuous variables were categorized	Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not apllicable
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	11 and 13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.